PRIMARY FALLOPIAN TUBE CARCINOMA:

OCCURRENCE, RISK AND PROGNOSTIC FACTORS

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ACADEMIC DISSERTATION

To be presented by permission of the Medical Faculty of the University of Helsinki,
for public criticism in the Lecture Hall 3, at Biomedicum, Helsinki
on 13th of April, 2007, at 12 o'clock noon

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ISBN 978-952-92-1818-9 (paperback)
ISBN 978-952-10-3816-7(pdf)
http:// ethesis.helsinki.fi
University Printing House
Helsinki 2007

To Teo, Taru and Krista

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by their Roman numerals (I-VI).

I Riska A, Leminen A, Pukkala E. Sociodemographic determinants of incidence of primary fallopian tube carcinoma, Finland 1953-97. Int J Cancer 2003; 104: 643-645.

II Riska A, Alfthan H, Finne P, Jalkanen J, Sorvari T, Stenman UH and Leminen A. Preoperative serum hCGß as a prognostic marker in primary fallopian tube carcinoma. Tumor Biol. 2006; 27:43-49.

III Riska A, Finne P, Alfthan H, Anttila T, Jalkanen J, Sorvari T, Stenman UH, Paavonen J, Leminen A. Past chlamydial infection is not associated with primary fallopian tube carcinoma. Eur J Cancer. 2006; 42:1835-1838.

IV Riska A, Finne P, Koskela P, Alfthan H, Jalkanen J, Lehtinen M, Sorvari T, Stenman UH, Paavonen J, Leminen A. Human papillomavirus infection and primary fallopian tube carcinoma: A seroepidemiological study. BJOG 2007; 114: 425-429.

V Riska A, Sund R, Pukkala E, Gissler M, Leminen A. Parity, tubal sterilization, hysterectomy and risk of primary fallopian tube carcinoma in Finland, 1975 – 2004. Int J Cancer 2007;120: 1351-1354.

VI Riska A, Pukkala E, Scelo G, Mellemkjaer L, Hemminki K, Weiderpass E, McBride ML, Pompe-Kirn V, Tracey E, Brewster DH, Kliewer EV, Tonita JM, Kee-Seng C, Jonasson JG, Martos C, Boffetta P, Brennan P. Second primary malignancies in females with primary fallopian tube carcinoma. Int J Cancer 2007; 120: 2047-2061.

ABBREVIATIONS

AFP	Alphafetoprotein
AUC	Area under the concentration-time curve
BMI	Body mass index
BRCA	Breast cancer antigen
CA125	Cancer antigen 125
CEA	Carcinoembryonic antigen
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CMI	Cell-mediated immunity
CPR	Finnish Central Population Registry
CRP	C reactive protein
CT	Chemotherapy
CTR	*Chlamydia trachomatis*
DFS	Disease-free survival
DNA	Deoxyribonucleic acid
EB	Elementary body
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
FIGO	International Federation of Gynecology and Obstetrics
FITC	Fluorescein isothiocyanate
GM	Grand multipara
hCG	Human chorionic gonadotropin
hCGβ	Beta subunit of hCG
hCGcf	Core fragment of hCG beta
HILMO	Hospital Discharge Registry
HPV	Human papillomavirus
Hsp	Heat shock protein
HSV	*Herpes simplex* virus
IARC	International Agency for Research on Cancer
IgG	Immunoglobulin G
kDA	KiloDalton
LH	Luteinizing hormone
LPS	Lipopolysaccharide
M	Menarche

MIF	Micro-immunofluorescence
MOMP	Major outer membrane protein
MP	Menopause
MRI	Magnetic resonance imaging
MS	Median survival
OC	Oral contraceptive
OR	Odds ratio
ORF	Opening reading frame
OS	Overall survival
PCR	Polymerase chain reaction
PFTC	Primary fallopian tube carcinoma
PID	Pelvic inflammatory disease
RB	Reticulate body
RNA	Ribonucleic acid
RR	Risk ratio
RT	Radiation therapy
SC	Squamous cell carcinoma of the uterine cervix
SEER	Surveillance, Epidemiology, and End Results program
SIR	Standardized incidence ratio
STAKES	National Research and Development Centre
STI	Sexually transmitted infection
TATI	Tumor-associated trypsin inhibitor
TGFβ	Transforming growth factor beta
VLP	Virus-like particle
WHO	World Health Organization

ABSTRACT

The aim of the study was to clarify the occurrence, and etiological and prognostic factors of primary fallopian tube carcinoma (PFTC). We studied the sociodemographic determinants of the incidence of PFTC in Finland and the role of chlamydial infections and human papillomavirus infections as risk factors for PFTC. Serum tumor markers were studied as prognostic factors for PFTC. We also evaluated selected reproductive factors (parity, sterilization and hysterectomy) as risk or protective factors of PFTC. The risks of second primary cancers after PFTC were also studied.

The age-adjusted incidence of PFTC in Finland increased from 1.2 per 1,000,000 in 1953–57 to 5.4 per 1,000,000 in 1993–97. The incidence rate was higher in the cities, but the relative rise was higher in rural areas. Women in the two highest social classes showed a 1.8–fold incidence compared with those in the lowest. Women in agriculture and those not working outside the home showed only half the PFTC incidence of those in higher socioeconomic occupations.

Pretreatment serum concentrations of hCGβ, CA125 and TATI were evaluated as prognostic markers for PFTC in a study including 60 patients. Elevated hCGβ values (above the 75th percentile, 3.5 pmol/L; OR 2.49, 95% CI 1.22–5.09), stage (OR 2.47, 95% CI 1.21–5.02) and histology (OR 2.71, 95% CI 1.26–5.83) were strong independent prognostic factors for PFTC.

Chlamydial and human papillomavirus (HPV) infections were studied in two separate seroepidemiological case-control studies with 78 PFTC patients. The incidence of women with positive HPV or chlamydial serology was the same in PFTC patients and in the control group and was not found to be a risk factor for PFTC.

The effects of parity, sterilization and hysterectomy on the risk of PFTC were studied in a case control-study with 573 PFTC cases from the Finnish Cancer Registry and ten age-matched controls from the Finnish Central Population Register. In multivariate analysis parity was the only significant protective factor as regards PFTC, with increasing protection associated with increasing number of deliveries (OR for 1 or 2 deliveries 0.63, 95% CI 0.44–0.91; and for $\geq$ 3 deliveries 0.32, 95% CI 0.19–0.52). In univariate analysis sterilization gave borderline protection against PFTC (OR 0.58, 95% CI 0.33–1.00) and the protective effect increased with time since the operation. The OR for PFTC after previous

breast cancer was 1.69 (95% CI 1.08–2.67) and after other cancers, 1.23 (95% CI 0.79–1.91).

Finally, the possible risk of a second primary cancer after diagnosis and treatment of PFTC in a cohort of 2084 cases from 13 cancer registries followed for second primary cancers within the period 1943–2000 was studied. In PFTC patients, second primary cancers were 36% more common than expected (SIR 1.36, 95% CI 1.13–1.63). The SIR for second cancer (all sites combined) was highest if the time since PFTC was more than 10 years, if age at PFTC diagnosis was less than 60 years or the year of PFTC diagnosis was before 1984. Significant increases were detected for non-lymphoid leukemia (SIR 3.7, 95% CI 1.0–9.4), for bladder cancer (2.8, 95% CI 1.0–6.0), for colorectal cancer (1.7, 95% CI 1.0–2.6), for breast cancer (1.5, 95% CI 1.1–2.2) and for lung cancer (1.8, 95% CI 0.9–3.2). Significant risks were detected for colorectal cancer during the second to fifth year after PFTC diagnosis, for non-lymphoid leukemia during the second to tenth year and for breast cancer after follow-up of 10+ years. The excess of colorectal and breast cancers after PFTC may indicate common effects of earlier treatments, or they could reflect common effects of lifestyle or genetic, immunological or environmental background.

In conclusion, the incidence of PFTC has increased in Finland, especially in higher social classes and among those in certain occupations. Secretion of hCGβ reflects the aggressiveness of this cancer. Serum hCGβ is a good prognostic marker and elevated levels reflect a worsened prognosis. The study findings suggest that PFTC is a disease with a multi-etiological background. Parity is a clear protective factor, as is previous sterilization, whereas factors other than infectious ones will have to be determined as possible risk factors of this disease. After PFTC there is a risk of second primary cancers, especially non-lymphoid leukemia, bladder, colorectal, breast, lung cancers.

INTRODUCTION

Primary fallopian tube carcinoma (PFTC) is one of the rarest carcinomas of the female genital tract and therefore it has been poorly studied. Because the incidence of PFTC has been increasing (Clayton et al. 2005) and the true incidence is probably underestimated (McMurray et al. 1986), there is a need for clinical study of its occurrence, and possible risk, prognostic and protective factors.

Primary fallopian tube carcinoma resembles ovarian cancer. The fallopian tube and ovary both develop from the Müllerian duct in organogenesis, the two diseases have a similar pattern of spread, they are diagnosed and treated similarly and the prognosis is also alike. However, in some aspects they behave differently. The earlier lymphatic spread of PFTC has been emphasized in many studies (Baekelandt et al. 1993). There are no studies on the prognostic significance of tumor markers other than CA125, no studies on the connection between chlamydial or human papillomavirus infections and PFTC, nor any studies on the effects of parity, earlier hysterectomy or sterilization on the risk of PFTC. Nor have second primary cancers occurring after PFTC been studied. The present study was designed to clarify these aspects.

REVIEW OF THE LITERATURE

1. OVERVIEW AND HISTORICAL ASPECTS

Primary fallopian tube carcinoma was first described by Renaud in 1847. According to Ricci, a case recorded by Renaud is in an unpublished manuscript in the library of the Royal College of Surgeons (Ricci 1945). Later it was reported by Rokitansky in 1861, but it was Orthmann who described PFTC as its own disease entity in 1886 (Orthmann 1888). In 1898 Falk used cul-de-sac puncture to aspirate the contents of a carcinomatous tube adherent to the pelvic peritoneum, and made the first preoperative diagnosis of PFTC (Southwood 1956). So far, fewer than 2500 cases have been reported in different studies worldwide, most of the reports being case-reports.

Primary fallopian tube carcinoma is a rare disease, constituting about 1% of female genital tract malignancies (Nordin 1994). The incidence rate of PFTC is 14% higher among Caucasian women (including Hispanics) than in African Americans (Rosenblatt et al. 1989). During the period 1995–99 the SEER program reported an age-adjusted incidence rate of 3.3/1,000,000 among Caucasian women (National Cancer Institute 2001). In Denmark, the incidence rate around 1980 was 2.9/1,000,000 (Pfeiffer et al. 1989). So far, the incidence rates over longer time periods have not been studied. Little is known about the epidemiology of PFTC. The risk and protective factors have been regarded as being similar to those of ovarian cancer. From epidemiological studies on ovarian cancer it is known that parity, use of oral contraceptives (OCs), breast-feeding, sterilization and hysterectomy are protective factors, whereas early age at menarche and late age at menopause are risk factors, and age, infertility and infertility treatments may be risk factors to some extent (Irwin et al. 1991; Hankinson et al. 1993; Hankinson et al. 1995; Riman et al. 1998; Auranen et al. 2005). Furthermore, women with a family history of breast/ovarian cancer have an increased risk of ovarian cancer (Narod 2006).

Two-thirds of PFTC patients are postmenopausal. The mean age of PFTC patients varies in different studies, being 60–69 years. The association with low parity (nulliparity in 17–45% of PFTC patients) (Eddy et al. 1984; Rosenblatt et al. 1989; Hellstrom et al. 1994) and the high incidence of histological and/or gross evidence of old pelvic inflammatory disease (PID) has been reported in many articles (Peters et al. 1988; Demopoulos et al. 2001). An initial connection between PFTC and tuberculous salpingitis was reported by Gungor et al. (2003), but no other precise infectious agent has been verified.

2. CLINICAL FEATURES

2.1. Symptoms and signs

The most common presentation of PFTC is postmenopausal vaginal bleeding and discharge (50–60%), followed by abdominal pain (30–49%) and abdominal mass (12–75%) (Ajithkumar et al. 2005; Clayton et al. 2005). Abdominal pain may be colicky because of forced tubal peristalsis. In 1916, Latzko called attention to a triad of intermittent profuse serosanguinous vaginal discharge, colicky pain relieved by discharge, and abdominal or pelvic mass, reported to present in 15% of PFTC patients. Hydrops tubae profluens – a pathognomic feature – implies intermittent discharge of clear or blood-tinged fluid spontaneously or on pressure, followed by shrinkage of the adnexal mass. However, this occurs in only 5 to 9 % of the patients (Nordin 1994; Ajithkumar et al. 2005). Many PFTC patients are asymptomatic and a delay between the first symptoms and diagnosis appears to be common. Symptoms connected to PFTC in different studies (Nordin 1994; Alvarado-Cabrero et al. 1999; Baekelandt et al. 2000; Obermair et al. 2001; Benoit and Hannigan 2006) are presented in Table 1.

Table 1. Symptoms connected to PFTC

Presenting symptom	%
Postmenopausal or abnormal vaginal bleeding	35–60
Abdominal pain	30–49
Abnormal Pap smear	10–36
Pelvic mass felt clinically	12–61
Abdominal distension	14–23
Latzko triad	15
Hydrops tubae profluens	5–9
Urinary urgency	8
Acute abdomen	5

2.2. Diagnosis

Correct preoperative diagnosis of PFTC is reported in 0.3–15% of cases (Alvarado-Cabrero et al. 1999; Santana et al. 2003; Ajithkumar et al. 2005). It has been speculated that when compared with ovarian cancer, PFTC would be more often diagnosed at an earlier stage owing to abdominal pain secondary to tubal distension (McMurray et al. 1986; Peters et al. 1988; Gadducci et al. 2001). However, there are no real studies on this issue. In 10% to 36%

of patients, abnormal cervical cytology in Pap smear tests representing adenocarcinoma is detected (Peters et al. 1988; Rahimpanah and Reid 2000; Obermair et al. 2001) and in 31% of the patients endometrial curettage shows adenocarcinoma (Baekelandt et al. 2000).

Ultrasonography in the diagnosis of PFTC is of limited value. There are some reports of adnexal masses with sausage-shaped structures with a cogwheel appearance inside, separate from the ovaries and uterus, but the exact nature of the lesion was not depicted before the operation (Kol et al. 1990; Yuen et al. 2002; Haratz-Rubinstein et al. 2004). Transvaginal color Doppler ultrasonography was an improvement, showing low vascular impedance and neovascularization, especially in papillary protrusions in the fallopian tubes (Kurjak et al. 1998). A study with three-dimensional power Doppler ultrasonography was even more accurate, showing arteriovenous shunts, microaneurysms, tumoral lakes, blind ends and dichotomous branching in all 5 PFTC cases (Kurjak et al. 2000). Some case reports of exact diagnoses with computed tomography (Santana et al. 2003) or with magnetic resonance imaging (MRI) exist (Mikami et al. 2003; Takagi et al. 2003; Hosokawa et al. 2006). Usually, PFTCs show as small cystic or solid masses that typically are sausage-shaped in MRI.

Niloff et al. pioneered research into tumor markers of PFTC in 1984. They described elevated CA125 levels in four patients with PFTC, associated with recurring disease (Niloff et al. 1984). Circulating levels of CA125 are increased in 65–80% of PFTC patients preoperatively (Takeshima et al. 1997; Baekelandt et al. 2000; Hefler et al. 2000). Concentrations of CA125 have been reported to be elevated in 20% of cases of stage I disease and in 75%, 89% and 100% in cases at stages II, III and IV, respectively (Takeshima et al. 1997).

2.3. Histopathology

Normal fallopian tube walls are constructed of three layers: the outer serosa layer, the muscularis containing an outer thinner longitudinal layer and an inner circular muscular layer, and the mucosa. The mucosal lining is composed of at least three types of cells: ciliated cells, the wave of which is directed towards the uterus, and nonciliated cells, i.e. secretory cells and intercalary (peg) cells that may be a variant of the secretory cells. Below the surface epithelium there are often stromal cells that can undergo decidual differentiation, e.g. in pregnancy. The epithelial cells undergo changes during the menstrual cycle in

response to changes in hormone levels, particularly those of estrogen (Ross et al. 2002). Fallopian tube carcinomas spread to adjacent organs, the peritoneum and regional lymph nodes. In many cases carcinomas involve both the tube and the ovary and it may be difficult to determine the organ of origin. In order to be regarded as a primary fallopian tube carcinoma the main tumor has to lie within the tube or its fimbrial end, a transition from benign to malignant epithelium should be visible and the ovaries/uterus should be normal or, if not, the condition must be clearly different from the fallopian tube lesion (Tavassoli et al. 2003). In 10–25% of patients both fallopian tubes are affected (Sedlis 1978; Yoonessi 1979).

The majority of fallopian tube malignancies are adenocarcinomas. The most common histological subtype is serous adenocarcinoma (50–80% of cases), followed by endometrioid, mucinous and other subtypes including clear cell, transitional and undifferentiated variants (Alvarado-Cabrero et al. 1999; Baekelandt et al. 2000). Rare types of cancers include sarcomas, germ cell tumors, lymphomas and malignant müllerian tumors (Coppleson 1992). There is no generally agreed grading system for fallopian tube carcinoma. The three-tiered system employed is based on the extent of the solid component and cellular atypia.

2.4. Staging

In 1991, the International Federation of Gynecology and Obstetrics (FIGO) established a staging classification for PFTC (Table 2). The distribution of different stages in different studies is summarized in Table 3.

Table 3. Distribution (%) of clinical stages (0–IV) in patients with PFTC

Reference	**Year**	***n****					
			0	**I**	**II**	**III**	**IV**
Eddy et al.	1984	71	6	20	27	34	13
Peters et al.	1988	115		34	23	22	3
Hellström et al.	1994	128	1	56	23	14	6
Rosen et al.	1998	143		42	19	26	12
Wolfson et al.	1998	72		33	28	33	6
Rauthe et al.	1998	37		46	19	32	3
Baekelandt et al.	2000	151	6	27	21	34	11
Hefler et al.	2000	53		30	13	47	9
Gadducci et al.	2001	88		24	24	49	3

*Number of PFTC patients in different studies

Table 2. FIGO staging (1991) of PFTC

Stage	0	Carcinoma *in situ* (limited to tubal epithelium)
Stage	**I**	Growth limited to the fallopian tubes
	Ia	Growth limited to one fallopian tube; no ascites; no tumor on the external surface; tubal serosa intact
	Ib	Growth limited to both fallopian tubes; no ascites; no tumor on the external surface; tubal serosa intact
	Ic	Either stage Ia or Ib, but with tumor on the surface of one or both fallopian tubes; tubal serosa ruptured or with ascites present containing malignant cells, or with positive peritoneal cytology
Stage	**II**	Growth involving one or both tubes with pelvic extension
	IIa	Extension or metastases to the uterus and/or ovaries
	IIb	Extension to the other pelvic tissues
	IIc	Tumor either IIa or IIb or with ascites present containing malignant cells or with positive peritoneal washings
Stage	**III**	Tumor involves one or both tubes with peritoneal implants outside the pelvis, including superficial liver metastasis, and/or positive retroperitoneal or inguinal nodes. Tumor limited to pelvis except for histologically proven extension to small bowel or omentum
	IIIa	Tumor grossly limited to pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
	IIIb	Tumor involving one or both fallopian tubes with grossly visible, histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Lymph nodes negative
	IIIc	Abdominal implants > 2 cm in diameter and/or positive retroperitoneal or inguinal nodes
Stage	**IV**	Growth involving both tubes with distant metastases including parenchymal liver metastases. If pleural effusion is present, fluid must be positive cytologically for malignant cells

2.5. Comparison of characteristics of PFTC and ovarian cancer

Primary fallopian tube carcinoma and epithelial ovarian cancer resemble each other in many ways. In Table 4 these characteristics are summarized (Peters et al. 1988; Hellstrom et al. 1994; Pectasides et al. 1994; McGuire et al. 1996a; McGuire et al. 1996b; Rosen et al. 1998; Wolfson et al. 1998; Baekelandt et al. 2000; Hefler et al. 2000; Gadducci et al. 2001; Kosary and Trimble 2002; du Bois et al. 2003; Ozols et al. 2003; Trimbos et al. 2003; Pectasides et al. 2006).

Table 4. Frequency (%) of characteristics of PFTC and EOC*

	PFTC	EOC
Histology		
Serous	50–80	52–80
Endometrioid	8–50	13–24
Mixed	4–17	3–9
Undifferentiated	8–11	1–2
Clear cell	2	4–12
Transitional	11	1–2
Mucinous	3–8	2–20
Grade		
1	15–20	8–20
2	20–30	30–38
3	50–65	48–54
Stage		
I	20–56	12
II	17–27	9–11
III	14–49	63–67
IV	3–13	14–17
Overall 5-year survival	22–57	50–82

*EOC= epithelial ovarian cancer

2.6. Natural course and the pattern of spread

Because of its frequently observed cardinal symptoms, i.e. painful tension in the tubes and an abnormal discharge of serous fluid, 17-56% of cases of PFTC are at stages I and II at diagnosis compared with ovarian carcinomas, in which two thirds are at stages III and IV at diagnosis. However, there are suggestions that advanced carcinoma of the tubes could be misdiagnosed as ovarian adenocarcinoma (Benedet et al. 1977), which would account for the lower incidence of advanced stages of the disease at diagnosis. The pattern of spread of PFTC has long been considered to be similar to that of ovarian carcinoma, with

intraperitoneal spread being the most frequently encountered (Wolfson et al. 1998). There is often intraperitoneal spread before the invasion of the ovaries. When direct invasion and transluminal spread occurs, it involves the serosae of the ovaries, uterus and intestines (Sedlis 1978). Lymph node involvement appears to be more common in PFTC than in ovarian carcinoma. The major lymphatic channels of the fallopian tube drain to the para-aortic nodes, whereas the medial portion occasionally drains via the lymphatics of the round ligaments to the inguinal region. Lymph node involvement occurs in 42 to 59% of PFTC patients, with almost equal involvement of para-aortic and pelvic nodes (Klein et al. 1994; di Re et al. 1996).

2.7. Associated pathologies and hereditary risk of PFTC

In 11 to 15% of PFTC patients there has been another malignancy before the diagnosis of PFTC (Alvarado-Cabrero et al. 1999; Baekelandt et al. 2000; Carcangiu et al. 2004; Clayton et al. 2005). In the study by Alvarado-Cabrero, 11 of 103 cases (11%) had had an earlier breast cancer. This study suggested that the association between breast and gynecological malignancies was a result of their similar hormone-responsiveness. Baekelandt et al. (2000) detected eight breast cancers, two cancers of the colon, and twelve second gynecological cancers among 151 PFTC patients. In a study by Aziz et al. (2001) an increase in the risk of ovarian cancer (RR = 2.2) and of early-onset breast cancer (RR = 2.4) was observed in the first-degree relatives of patients with PFTC. Altogether, 11% of PFTC patients were BRCA1 mutation carriers and 5% carried BRCA2. The authors suggested that PFTC should be considered to be a clinical component of the hereditary breast-ovarian cancer syndrome, and it may be associated with BRCA1 and BRCA2 mutations (Aziz et al. 2001). The frequency of proliferative lesions of the tubal epithelium is increased in BRCA1 mutation carriers (Carcangiu et al. 2004). Leeper et al. found three PFTC cases in a study in which they examined fallopian tubes in 30 patients with BRCA1 or BRCA2 gene mutations, or a family history indicating susceptibility to ovarian and breast cancer (Leeper et al. 2002). In 2005, Cass et al. reported a 43% rate of BRCA mutations in PFTC patients (11/28 BRCA1 and 1/28 BRCA2). Those with BRCA mutations were also younger than those with sporadic PFTC (Cass et al. 2005). For comparison, the rate of BRCA mutations among ovarian cancer patients is 3 to 10% (Dorum et al. 1999; Malander et al. 2004).

2.8. Survival and prognostic factors

Because PFTC is rare and treatment modalities vary between different countries, survival rates also fluctuate widely. Lymphangial spread at early stages is typical of PFTC and worsens the prognosis. Five-year overall survival rates vary between 22 and 57%. Survival rates according to different stages are summarized in Table 5.

2.8.1. Stage

In almost all studies concerning prognostic factors, stage has been significant (Table 5): patients with PFTC who have local disease survive better than those with advanced stages. For patients with stage I disease, the depth of tumor infiltration in the tubal wall and intraoperative tumor rupture are of independent prognostic significance (Baekelandt et al. 2000). The absence of closure of the fimbriated end of the fallopian tube has been of marginal significance as regards worse prognosis (Alvarado-Cabrero et al. 1999).

2.8.2. Size of the residual tumor

Residual tumor size is a very strong prognostic factor. In most studies residual tumor size has been divided into two groups: more or less than 1–2 cm (Peters et al. 1988; Rosen et al. 1999; Baekelandt et al. 2000; Gadducci et al. 2001). Patients with stage III-IV disease are reported to have a 5-year survival rate of 55% with a residual tumor size of less than 1 cm, compared with 21% for those with a larger residual tumor (Gadducci et al. 2001) (Table 6).

2.8.3. Grade

The prognostic significance of tumor grade is controversial. In most studies grade of the tumor is marginally prognostic, remaining non-significant in statistical analyses (Hellström et al. 1994; Hefler et al. 2000; Gadducci et al. 2001). However, in a study by Rosen and co-authors, grade was an independent prognostic factor: grade I tumors were associated with a 5-year survival rate of 58%, grade II, 47% and grade III tumors, 33% ($p = 0.03$) (Rosen et al. 1999). In a study carried out by Gadducci et al. the overall 5-year survival rate was 45% as regards grade III tumors and 80% as regards grade I-II tumors ($p = 0.0038$) (Gadducci et al. 2001).

2.8.4. Histology

The effect of histological subgroup on the prognosis of PFTC patients has also been investigated in some studies, but no statistically significant differences have been detected (Alvarado-Cabrero et al. 1999; Gadducci et al. 2001). In the study by Alvarado-Cabreros

Table 5. Five-year survival rates (%) of PFTC patients according to stage

Reference	*n**	Stage					Overall	Significance[#]
		0	I	II	III	IV		
Eddy et al. 1984	71	75	34	32	7 (III and IV)			
Peters et al. 1988	115		61	29	17			$p<0.0001$
Hellström et al. 1994	127		72 (Ia), 33 (Ib-c)	30	24	13		$p=0.001$
Wolfson et al. 1998	72		48	II-IV 35				$p=0.04$
Rosen et al. 1998	143		59 (I and II)		19 (III and IV)		43	$p<0.00001$
Baekelandt et al. 2000	151	87	73	37	29	12		
Schneider et al. 2000	19		80		none	none	22	
Gadducci et al. 2001	88		85 (I and II)		34 (III and IV)		57	$p=0.0001$
Obermair et al. 2001	36		62		53 (II-IV)			$p=0.03$
Kosary et al. 2002	416		95	75	69	45		

*Number of PFTC patients, [#]Difference in survival among surgical stages

Table 6. Survival of PFTC patients according to size of the residual tumor

Reference	*n**	Size of the residual tumor	Survival rate	p-value
Eddy et al. 1984	71	No gross residual tumor	5-year survival 29%	
		Residual tumor no tumor vs. > 2cm Residual tumor <2cm vs. >2 cm	29% vs. 7% 15% vs. 7%	0.04
Peters et al. 1988	115	Residual tumor < 2 cm		<.001
Rosen et al. 1999	143	Residual tumor <2cm vs. > 2 cm	MS time 35 months vs.11 months	0.03
Baekelandt et al. 2000	151	No residual tumor	5-year survival 63%	
		Residual tumor present	5-year survival 14%	<0.0001
Gemignani et al. 2000	24	Residual tumor < 1cm	Median progression free, 3 years 67%	
		Residual tumor > 1cm	Median progression free, 3 years 45%	
Gadducci et al. 2001	88	Residual tumor <1 cm (stage III-IV)	5-year survival 55%	
		Residual tumor >1cm (stage III-IV)	5-year survival 21%	p=0.0169
Obermair et al. 2001	36	No residual tumor	5-year survival 60%	
		Residual tumor present	5-year survival 0%	p=0.02

* Number of PFTC patients, MS= median survival

et al. better prognosis of patients with endometrioid versus serous or transitional carcinomas correlated with the lower average stage of the former, and was not observed when the analysis was restricted to stage I and IIa cases (Alvarado-Cabrero et al. 1999).

2.8.5. Age

The prognosis of PFTC patients over 60 years of age (compared to younger patients) is worsened in nearly half of the studies (Peters et al. 1988; Wolfson et al. 1998; Alvarado-Cabrero et al. 1999; Baekelandt et al. 2000; Hefler et al. 2000).

2.8.6. Lymph node status and ascites

Studies of primary lymph node status during operation as a prognostic marker are sparse. In one study from Italy lymph node metastasis and positive peritoneal cytology were predictive for worse prognosis of PFTC in univariate analysis (Cormio et al. 1996). In another study from Italy, patients with a negative lymph node status had a median survival (MS) of 76 months, compared with only 33 months in patients with node metastases (di Re et al. 1996). In Heflers study lymph node involvement was not associated with survival, nor was it correlated with pre-treatment CA125 level (Hefler et al. 2000). In the study of Peters the presence of ascites was a marker of a poor prognosis (Peters et al. 1988).

2.8.7. Hydrosalpinx-like appearance

Closure of the fimbriated end of the fallopian tube and its possible effect on the prognosis of PFTC has been debated. Theories on the spread of malignant cells through the open fallopian tube to the peritoneal lining and its effect on survival have been presented. Absence of closure of the fimbriated end has been associated with shorter survival. In a study by Alvarado-Cabrero and co-workers (1999) and in another by Baekelandt et al. (2000), a hydrosalpinx-like appearance affected 5-year survival, the rates being 63% and 37% (p=0.0227), when present (in 30% of the patients) and absent, respectively (Baekelandt et al. 2000).

2.9. Treatment

Surgery is the definite primary treatment and it involves total abdominal hysterectomy with bilateral salphingo-oophorectomy, infracolic omentectomy and appendectomy. Pelvic and para-aortic lymphadenectomy and, depending of the extent of the disease, careful debulking is obligatory. Obtaining a sample for peritoneal cytology at the beginning of laparotomy is important (DiSaia and Creasman 2002).

Because of the rarity of the disease, prospective controlled trials of treatment regimens have been impossible to conduct. In earlier decades radiation therapy (RT) was the traditional adjuvant therapy for PFTC. It has been given in different forms: external whole abdominal or pelvic radiation, treatment with intraperitoneal isotopes, and vaginal and uterine implantation (Nordin 1994). Today RT should no longer be used except for palliation of specific symptoms, because of its low efficacy and a high rate of serious complications (Baekelandt et al. 2000; Gadducci 2002). As adjuvant therapy, pelvic RT has not improved survival and a large proportion of patients with whole abdominal RT will develop recurrences outside the abdominal cavity and will also have severe gastrointestinal complications (Baekelandt et al. 2000).

Regarding chemotherapy (CT), again because of the rarity of the disease, very few data are available. Because of the high risk of distant metastases even after complete surgical resection, adjuvant therapy is usually suggested, even among patients with early disease. An exception is patients with carcinoma confined to the tube, not penetrating the serosal surface and without intraoperative tumor rupture. Such patients may not require adjuvant treatment (Baekelandt et al. 2000). The current CT lines are summarized in Table 7 (Gadducci 2002, Pectasides et al. 2006).

Table 7. Chemothereapy of PFTC

Stage	Treatment
Ia-Ib, optimal surgical staging, no pre- or intraoperative rupture	No further treatment
Ia-Ib, suboptimal surgical staging, pre- or intraoperative rupture	Paclitaxel (175 mg/m^2)-carboplatin (AUC 5-6) every 3 weeks for 3–6 cycles
Ic-IV	Paclitaxel (175 mg/m^2)-carboplatin (AUC 5-6) every 3 weeks for 6–8 cycles
For relapse and for second-line therapy	
Patients who failed paclitaxel-based chemotherapy	Docetaxel (75–100 mg/m^2)-carboplatin (AUC 5) every 3 weeks
Platinum- and paclitaxel-resistant disease	Liposomal doxorubicin (50 mg/m^2) every 4 weeks Topotecan (1.5–2.0 mg/m^2) a day for 3–5 days every 3 weeks

2.10. Tumor markers as diagnostic and prognostic factors in PFTC

2.10.1. General aspects

Tumor markers are substances that can be identified in body fluids (serum and urine) and tissues and are used for diagnosis, follow-up and as prognostic markers among patients with cancer. They can be divided into three categories: 1) oncodevelopmental antigens, 2) cancer-associated antigens, and 3) tumor markers representing biochemical and metabolic alterations, usually as a reaction of the host against the tumor. Tumor markers may also be classified as tumor-specific markers, organ-specific markers and reaction products against cancer or cancer-associated metabolic changes. Many tumor-associated antigens are oncofetal, such as carcinoembryonic antigen (CEA), alphafetoprotein (AFP) and human chorionic gonadotropin (hCG). Cancer-associated antigens may be defined as substances that are either newly acquired during the neoplastic process or that reflect augmentation of certain, usually undetectable, normal cell antigens. The first cancer-associated antigens were characterized in 1956 by Whitebsky, many of them being markers of ovarian cancer (Rose et al. 1956). A large number of cancer-associated antigens and oncodevelopmental antigens associated with ovarian cancer have been identified since then; today the most commonly used are cancer antigen 125 (CA125), hCG, TATI and AFP. Only CA125 as a tumor marker of PFTC has been studied earlier.

2.10.2. Carcinoma antigen 125 (CA125)

CA125 is a cancer-associated antigen defined by a murine monoclonal antibody (OC125, IgG1) which was produced by immunizing mice with an ovarian serous cystadenocarcinoma cell line, OVCA433 (Bast et al. 1981).

The antigen has been detected in tissues derived from coelomic epithelium in the embryo and adult, including the pleura, pericardium, peritoneum, fallopian tube, endometrium and endocervix. Outside this lineage, CA125 has also been detected in tracheobronchial epithelium and glands, amnion, amniotic fluid, milk, cervical mucus and seminal fluid (DiSaia and Creasman 2002).

Serum concentrations of CA125 are measured by immunoradiometric assay, introduced by Bast et al. in 1983. They suggested a 35 U/ml cut-off value for normal controls (Bast et al. 1983). Niloff et al. were the first to describe elevated CA125 levels in PFTC (Niloff et al.

1984) and Lootsma-Miklosova et al. were the pioneers in monitoring changes in CA125 levels during treatment and recurrence (Lootsma-Miklosova et al. 1987). In 1990, Rosen et al. studied pre- and postoperative concentrations of CA125 in PFTC and in contrast to their earlier experiences with ovarian cancer, they did not find a correlation with prognosis, but a trend for a positive correlation between FIGO stage and preoperative CA125 values was observed (Rosen et al. 1994). In a study among 40 PFTC patients in Norway, there were strong correlations between preoperatively elevated CA125 levels and more advanced disease, and the presence of residual disease (Baekelandt et al. 2000). In the same year Hefler et al. studied the clinical value of assay of serum CA125 in PFTC and reported that serum CA125 is an additional independent prognostic factor of disease-free survival (DFS) and overall survival (OS) in patients with the disease (Hefler et al. 2000). The studies mentioned above are the only ones conducted concerning CA125 and PFTC.

2.10.3. Human chorionic gonadotropin beta

Human chorionic gonadotropin (hCG) is a glycoprotein consisting of two polypeptide subunits, i.e. the α- and β-subunit. Luteinizing hormone (LH) and hCG mediate their activity through the same receptor. The latter is produced by placental trophoblasts and it is a very good marker for monitoring pregnancy. Placental and trophoblastic tumors nearly always produce hCG, but it is also secreted in non-trophoblastic malignancies. Serum from many patients with non-trophoblastic tumors contains hCG immunoreactivity, which with a few exceptions consists of the free β-subunit of hCG (hCGβ). The subunits lack hCG activity but hCGβ has been shown to enhance the growth of tumor cells in culture by preventing apoptosis (Butler et al. 2000). The half-times of hCG and hCGβ differ, being longer for hCGβ than for hCG. For hCG the rapid half-time is 4 hours and the slow one 2.2 days. In contrast, hCGβ has a slow half-time of about 8 days and a rapid one of about 1 hour (Korhonen et al. 1997). This is very important to know when studying the percentual values of serum hCG and hCGβ in the follow-up of trophoblastic diseases. In Finland hCGβ in serum is quantified by means of a time-resolved immunofluorometric assay (Alfthan et al. 1988), with a detection limit of 0.5 pmol/L.

Elevated expression of hCGβ in serum, urine or tumor tissue is a strong indicator of poor prognosis in many non-trophoblastic tumors, such as colorectal (Lundin et al. 2001; Louhimo et al. 2002), ovarian (Vartiainen et al. 2001) and renal cell carcinoma (Hotakainen et al. 2002; Hotakainen et al. 2003). Elevated serum levels of hCGβ correlate with excretion

of the core fragment of hCGβ (hCGβcf), a degradation product of hCGβ passing into the urine (Alfthan et al. 1992). Elevated urinary levels of the core fragment of hCGβ reflect a worsened prognosis in vulvar and cervical carcinoma (Carter et al. 1994; Carter et al. 1995). In ovarian carcinoma, the 5-year survival rate was found to be 80% if serum hCGβ levels were normal, compared with 22% when they were elevated (Vartiainen et al. 2001).

2.10.4. Tumor-associated trypsin inhibitor (TATI)

Tumor-associated trypsin inhibitor is a low molecular weight (6 kDa) trypsin inhibitor, which was initially isolated from the urine of a patient with ovarian cancer (Stenman et al. 1982). The mean serum concentration of TATI in healthy individuals is 11 µg/L. It is rapidly cleared from the circulation by renal excretion, with a half-life of 6 minutes (Marks and Ohlsson 1983). Therefore, renal failure causes increased concentrations of TATI in the serum. It is expressed in several healthy tissues, especially in the gastrointestinal and urogenital tracts.

Levels of TATI in serum are increased in many benign conditions, e.g. pancreatitis, and in patients with severe injury and inflammatory disease. However, in patients with pelvic inflammatory disease, TATI concentrations start to increase only when serum levels of C-reactive protein (CRP) are clearly increased (Paavonen et al. 1989). Cancers originating from gastrointestinal and urogenital tissues often produce TATI. The increase is caused by production by the tumor, but an acute-phase reaction induced by tissue destruction associated with cancer invasion most likely contributes to the increased TATI concentrations seen in advanced disease. The strongest expression occurs in mucinous ovarian tumors, both benign and malignant (Halila et al. 1988; Koivunen et al. 1991). In mucinous ovarian cancer 45% of the cases already have increased TATI concentrations at stage I and the figure is 90–100% in stage IV disease. In non-mucinous cancers, TATI concentrations are elevated in high-grade tumors. Increased serum concentrations occur in 50–60% of patients with stage III-IV disease, and in these patients, an increased value before therapy is an independent prognostic factor for adverse outcome (Venesmaa et al. 1994).

2.11. *Chlamydia trachomatis* infection as a risk factor

2.11.1. Microbiology and clinical gynecological manifestations of chlamydiae

Chlamydiae are obligate intracellular gram-negative bacteria that replicate in membrane-bound vacuoles (inclusions) in the cytoplasm of eukaryotic cells. Chlamydiae can be divided

to four species: C.trachomatis, C.pneumoniae, C.psittaci, and C.pecorum. Chlamydiae are able to induce a variety of humoral and cell-mediated immune responses. Chlamydiae require living hosts for their replication because they lack many biosynthetic capabilities. Chlamydia has a very unique life-cycle with an extracellular infective elementary body (EB) and a non-infective intracellular reticulate body (RB) (Grayston and Wang 1975). The EB attaches to and enters the host cell. The chlamydial cell is surrounded by an envelope that consists of an outer membrane and an inner cytoplasmic membrane. The most prominent component of the chlamydial outer membrane of the EB is the major outer membrane protein (MOMP) (Caldwell et al. 1981; Wang et al. 1985), also found in the RB, comprising about 60% of the protein content. The MOMP plays a role in adhesion of *Chlamydia* to host cells.

*Chlamydia trachomatis (*CTR) species is divided into 18 human serotypes A, B, Ba, C, D, Da, E, F, G, H, I, Ia, J, K L1, L2, L2a and L3 (Grayston and Wang 1975). Serotypes A–K primarily infect columnar epithelium, causing mucosal infections. Serotypes B, Ba, C and D–K cause chlamydial urogenital infections as well as inclusion conjunctivitis, transmitted from the genital tract to the eye.

Infection with CTR is the one of the most common sexually transmitted infections (STIs), causing 90 million new infections each year worldwide. Acute genital tract infections include urethritis, cervicitis, salpingitis, endometritis and pelvic inflammatory disease (PID) – the major cause of tubal factor infertility and ectopic pregnancy. No long-lasting protective immunity against CTR develops during acute infections. Repeated or persistent infections, which provide an opportunity for long-term stimulation of the host with chlamydial antigens, result in tissue damage. Heat shock proteins (Hsps), found in chlamydial cell walls, play a crucial part in this damage.

2.11.2. Serological diagnosis of *C. trachomatis* infection

The micro-immunofluorescence (MIF) test and enzyme-linked immunoassays (EIAs) (Närvänen et al. 1998) are the serological methods for diagnosing chlamydial infections. The MIF test has been regarded as the golden standard for epidemiological research and is a sensitive and most specific method (Wang and Grayston 1970).

2.11.3. Chlamydia and gynecological cancer

Repeated or chronic chlamydial infection increases the likelihood of severe consequences. Chlamydial infection evokes both humoral and cell-mediated immune (CMI) responses. Chlamydial HSP60 may have an anti-apoptotic effect during persistent infection (Dean and Powers 2001). The accumulation of HSP60 in the cytoplasm of actively replicating cells may interfere with the apoptotic pathway. The concomitant expression of viral oncoproteins and/or the presence of mutations may lead to the ability to survive apoptotic stimuli, loss of replicative senescence, uncontrolled proliferation and finally neoplastic transformation (Di Felice et al. 2005). Studies connecting chlamydial infection and gynecological cancer are presented in Table 8 (Risch and Howe 1995, Koskela et al. 2000, Anttila et al. 2001, Wallin et al. 2002, Ness et al. 2003, Smith et al. 2004).

Table 8. Studies on *Chlamydia trachomatis* and gynecological cancer

Study	Study design	Result
Koskela et al. 2000	Prospective seroepidemiologic case-control study	Risk of SC, OR 2.2 (95% CI 1.3–3.5);*
Anttila et al. 2001	Seroepidemiologic case-control study	All serotypes increased the risk of SCC and serotype G most strongly, OR 6.6 (1.6–27)*
Wallin et al. 2002	Population-based prospective case-control study	RR of cervical cancer 17.1 (2.6–∞)*
Smith et al. 2004	Serologic case-control study	Increased the risk of SCC among HPV-positive women, OR 1.8 (1.2–2.7)
Risch, Howe 1995	Case-control study	History of PID increased the risk of ovarian cancer, OR 1.5 (1.1–2.1)*
Ness et al. 2003	Seroepidemiologic case-control study	Women with higher levels of *C. trachomatis* antibodies to serovar D had a 90% greater probability of having ovarian cancer, $p = 0.05$ *

*Adjusted for human papillomavirus (HPV); SC = squamous cell carcinoma

2.12. Human papillomavirus infection as a risk factor

2.12.1. HPVs

Papillomaviruses are small, non-enveloped, double stranded DNA viruses. The genome is circular and contains approximately 7900 base pairs (Chen et al. 1982). The genome of HPV contains approximately eight opening reading frames (ORFs), which are transcribed from a

single DNA strand. The ORFs code for two late structural proteins (L1 and L2) and six early (E) proteins. The protein coat (capsid) is composed of 72 capsomers consisting of L1 and L2 proteins. The role of the capsid is to protect the genome and to target cellular surface receptors involved in infection. The L1 protein can become assembled to virus-like particles (VLPs) when expressed in eukaryotic cells (Kirnbauer et al. 1992). These do not contain viral oncogenes and are not infectious (Kirnbauer et al. 1994).

To date, over 200 HPV types have been identified and approximately 40 types infect mucosal epithelia and are called genital HPVs (de Villiers et al. 2004). These types are further divided into high-risk types (cell transformation) and low-risk types (benign warts). Fifteen HPV types are classified as high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82), three are classified as probable high-risk types (26, 53 and 66) and 12 are classified as low-risk types (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and CP6108) (Munoz et al. 2003). The HPV binds to specific cell surface receptors and after attachment it enters the cell. Once the virus has penetrated the epithelium it establishes itself in the basal layers, where cell proliferation begins. When the infected cell divides, viral DNA is distributed in both daughter cells; in one that migrates upwards to start differentiation, and in the other that continues to divide in the basal layer. That cell becomes the reservoir for viral DNA, and explains the ability of HPV infection to persist for many years (Stubenrauch and Laimins 1999).

2.12.2. Epidemiology of genital HPV infections

Every year, about 400 million new HPV infections occur worldwide (WHO). Estimates of the population prevalence of HPV infection among women around the world range from 2% to 44% (Bosch and de Sanjose 2003). The life-time risk of HPV infection is high, the cumulative risk at three years of any HPV infection being 44% for women earlier being negative for HPV and 26% for detecting a type not present in the first positive sample (Woodman et al. 2001). Most HPV infections are transient, 80–90% spontaneously regressing in 2 years (Evander et al. 1995). Persistent infection with high-risk HPV is a major risk factor for cervical neoplasia and a cause of cervical cancer (Walboomers et al. 1999).

2.12.3. HPV serology

HPV serology is an important epidemiological tool for the assay of past and present HPV infections and for prediction of HPV-associated cancers. A serological assay based on HPV virus-like particles that correlates with type-specific detection of HPV infection, as

determined by detection of the viral genome, was established in 1994 (Kirnbauer et al. 1994). Nowadays, an enzyme-linked immunosorbent assay (ELISA) is used, employing a monoclonal antibody against human immunoglobulin G (IgG) and a goat anti-mouse IgG horseradish peroxidase conjugate. The sensitivity of HPV serology has been reported to be 50 to 75% (Kirnbauer et al. 1994; Kjellberg et al. 1999) and specificity for the sexually transmitted HPV types, 95–99% (Dillner et al. 1996). The natural history of the HPV serum antibody response is well known. Seroconversions against HPV16 capsids have been seen concomitantly with or within a few months following acquisition of HPV16 DNA (Wikstrom et al. 1995; af Geijersstam et al. 1998) and IgG antibody levels have been found to be stable over time even after more than a decade of follow-up (af Geijersstam et al. 1998). This is in line with the fact that IgG seropositivity to oncogenic genital HPVs strongly correlates with the lifetime number of sexual partners (Carter et al. 1996), but does not correlate with the number of recent partners (Wang et al. 2000), which would have been correlated if seropositivity had had more limited stability over time. We know that it is women with persistent type-specific positivity that are at increased risk of developing invasive cervical cancer (Wallin et al. 1999).

2.12.4. HPV and gynecological cancer

HPV infection is well established as an important factor in the pathogenesis of cervical neoplasia (Bosch et al. 2002). In 1983 the first isolation of an oncogenic virus type (HPV16) from cervical cancer was reported (Durst et al. 1983). An association has also been detected as regards vulvar and vaginal carcinomas (Madeleine et al. 1997; Daling et al. 2002).

HPV involvement in cancers of the upper genital tract (endometrial and ovarian cancers) has also been investigated, but the results have been highly controversial and are based mainly on DNA detection in tissue samples (Fujita et al. 1995; Czerwenka et al. 1996; Hording et al. 1997; Zimna et al. 1997; Chen et al. 1999; Hisada et al. 2001; Ip et al. 2002; Wu et al. 2003; Yang et al. 2003). There is only one serological study on HPV antibodies and the risk of endometrial and ovarian cancer and PFTC (Hisada et al. 2001). Studies concerning gynecological cancers and HPV are presented in Table 9.

3. ASSOCIATION BETWEEN PFTC AND SELECTED REPRODUCTIVE FACTORS

3.1. Effect of parity on gynecological cancer

Studies on parity and its influence on hormone-dependent gynecological cancers have consistently revealed the protective effect of parity on these cancers (Parazzini et al. 1989;

Table 9. Studies on HPV and gynecological cancer

Cancer	Study	Study material	Analyzed factor	Main results
Cervix	Bosch et al. 1995	1035 tissue samples from 22 countries	HPV DNA in tissues of invasive cervical cancers	93% of tissues were HPV DNA-positive (HPV16 50%, HPV18 14%)
Vulva (squamous)	Madeleine et al. 1997	Population-based case-control study (510 cases, 1403 controls)	Serum HPV-Ab, HPV DNA in tumor tissues	OR 18.8 for vulvar cancer among current smokers who were HPV16-seropositive (compared with never smokers who were HPV-seronegative)
Vagina (squamous)	Daling et al. 2002	Population-based case-control study (156 cases, 2041 controls)	Serum HPV-Ab, HPV DNA in tumor tissues	Serum HPV16 Ab-positivity was a risk factor for vaginal cancer OR 4.3 (95% CI 3.0–6.2)
Uterus	Fujita et al. 1995	98 endometrial lesions	HPV DNA in endometrial tissues	HPV16 DNA was present in 9% of endometrial adenocarcinomas
	Czerwenka et al. 1996	43 endometrioid carcinomas with squamous differentiation	HPV DNA in endometrial tissues	No evidence of high risk HPV DNA in tissue samples
	Hording et al. 1997	23 endometrial adenocarcinomas 50 cervical adenocarcinomas	HPV DNA in tissues	HPV DNA in 70% of cervical adenocarcinomas, and in none of the endometrial carcinomas
Uterus and ovary	Zimna et al. 1997	37 endometrial cancers 21 ovarian cancers	HPV DNA in tissues	HPV18 DNA in 30% of endometrial and in 40% of ovarian cancers
	Hisada et al. 2001	Prospective serological study (83 cervical, 34 endometrial, 35 ovarian cancer cases, 172 controls)	Serum HPV16-Ab	Cervical cancer OR 2.0 (1.0–3.4) Endometrial cancer OR 1.6 (0.64–3.8) Ovarian cancer OR 1.1 (0.43–2.8)
	Ip et al. 2002	55 endometrial adenocarcinomas 60 epithelial ovarian cancers	HPV DNA in tissues	HPV16 DNA in 9% of endometrial carcinomas and in 10% of ovarian cancers (5/60 HPV16 and 1/60 HPV18)
	Yang et al. 2003	95 cervical cancers 46 endometrial cancers 56 ovarian cancers	HPV16 and -18 DNA in tissues	HPV16 DNA present in 61% (cervical), 15% (endometrial) and 32% (ovarian); HPV18 DNA present in 23%, 1.8% and 0%, respectively
	Wu et al. 2003	54 ovarian cancers (50 epithelial) 30 nonmalignant ovarian tissues as controls	HPV16 DNA	HPV16 DNA positivity increased the risk; OR 16.7 (3.2–71.4)

Whittemore et al. 1992a; Lambe et al. 1996; McPherson et al. 1996), but only one earlier study has reported parity data on PFTC (Nordin et al. 1994). These investigators found a nulliparity rate of 27% and a mean parity of 1.7 among PFTC patients in a review including all articles and case reports published in the English literature from 1973 to 1992, but no study has been carried out to study the real effect of parity on PFTC.

Increasing parity lowers the risk of ovarian cancer, especially that of epithelial ovarian cancer (Whittemore et al. 1992a; Adami et al. 1994; Hinkula et al. 2006). Each full-term pregnancy diminishes the risk by 15 to 20% (Adami et al. 1994; Risch et al. 1994), the greatest protection being associated with the first term pregnancy (Whittemore et al. 1992a). The influence of age at first birth on ovarian cancer has been unclear (Riman et al. 1998). Some investigators have found a reduction of risk with older age at first birth and last birth (OR 0.57; 95% CI 0.36–0.90) (Titus-Ernstoff et al. 2001; Whiteman et al. 2003) or a risk increase with younger age at first pregnancy (OR 1.4, 95% CI 1.1–1.8), younger age at last pregnancy and with longer time since last pregnancy (Cooper et al. 1999). Other investigators have found a risk increase with older age at first birth (RR 4.18, ages 35–39 years, 95% CI 1.98–8.79) (Negri et al. 1991; Mogren et al. 2001). A recent study in Finland did not reveal any significance of age, but the incidence of ovarian cancer was 36% smaller among grand multiparous (GM) women compared with average Finnish women (Hinkula et al. 2006). In that study, parity above five births did not provide any additional protection versus that associated with 5 births.

Nulliparity and/or nulligravidity have been consistently associated with an increased risk of endometrial cancer (Salmi 1979; Parazzini et al. 1991; McPherson et al. 1996). In a study by Hinkula et al. in Finland, a large number of births, relatively old age at first delivery, a long birth period and a short premenopausal delivery-free period reduced the risk of postmenopausal endometrial cancer among GM women, emphasizing the protective role of progesterone and the stimulatory role of estradiol in the hormonal background of endometrial cancer (Hinkula et al. 2002).

Cervical adenocarcinoma constitutes up to 20% of all cervical cancers (Vesterinen et al. 1989; Leminen et al. 1990; Castellsague et al. 2006). Risk factors for this cancer have been regarded as being similar to those of endometrial cancer (Salmi 1979), but HPV infection appears to be the key risk factor for this cancer, as for cervical squamous cell cancer, HPV

type 18 being the most prominent among cervical adenocarcinomas (Leminen et al. 1991; Castellsague et al. 2006). Nulliparity has been considered to be a risk factor for cervical adenocarcinoma, whereas multiparity, especially among HPV-positive women, has been considered to be a risk factor for squamous cell carcinoma (Leminen et al. 1991; Munoz et al. 2002; Hinkula et al. 2004), these findings showing the difference in etiological factors between these two cancers.

Early first pregnancy and multiparity are known to reduce the risk of breast cancer, probably as a result of the hormonally induced differentiation of breast cells and the corresponding reduction in the number of susceptible cells (Mogren et al. 2001). Childbirth is followed by a short-term increase in the risk of breast cancer, followed by a long-term protective effect (Mogren et al. 2001).

Taken together, parity has various effects on the risk of different gynecological cancers, which could in part be explained by the hypotheses of incessant ovulation (Fathalla 1971) and raised gonadotropin (Cramer and Welch 1983). All gynecological cancers are members of the family of hormone-dependent cancers and birth may affect risk through hormonal influences. The incessant ovulation theory accords with the observed protective effect of interrupted ovulation as a result of increased parity, oral contraceptive use, or breast-feeding (Whittemore et al. 1992b). The gonadotropin hypothesis asserts that ovarian cancer is principally caused by high levels of gonadotropin that increase estrogen production and ovarian surface epithelial proliferation and malignant transformation. Pituitary secretion of gonadotropin generally increases during adulthood, but decreases during pregnancy; thus the protective effects of later childbirth are consistent with this hypothesis. One possible explanation for the pregnancy-reducing effect on the risk of ovarian cancer could be the high levels of progesterone during pregnancy, that induce apoptosis of transformed epithelial cells (Rodriguez et al. 1998). Pregnancy-dependent clearance of ovarian cells that have undergone malignant transformation was suggested by Adami et al. (Adami et al. 1994). Endometrial cancer risk may also be reduced by pregnancies through mechanical shedding of cells that have undergone malignant transformation (Lambe et al. 1999).

3.2. Sterilization

As early as in 1934 the first gynecologic laparoscopy was performed by Ruddock (Filshie 1999). The spring clip was first developed by Hulka and Clemens in 1974 and in the same

year research on the Filshie clip started and it was used in humans in 1975 (Filshie 1988). In the 1970s, the popularity of sterilization increased dramatically, because of legislation and attitudes. It also became easily available as a result of new surgical approaches, such as minilaparotomy and laparoscopy. In Finland sterilization became possible on request in 1970, and in 1985 the law changed, being more liberal. The frequency of sterilization has varied in recent decades in Finland, being 1560, 12 934 and 5906 sterilizations per year, respectively, in 1975, 1991 and 2003 (Figure 1). Part of this variation can be explained by the introduction of the levonorgestrel-releasing intrauterine device in 1986 (Luukkainen et al. 1990).

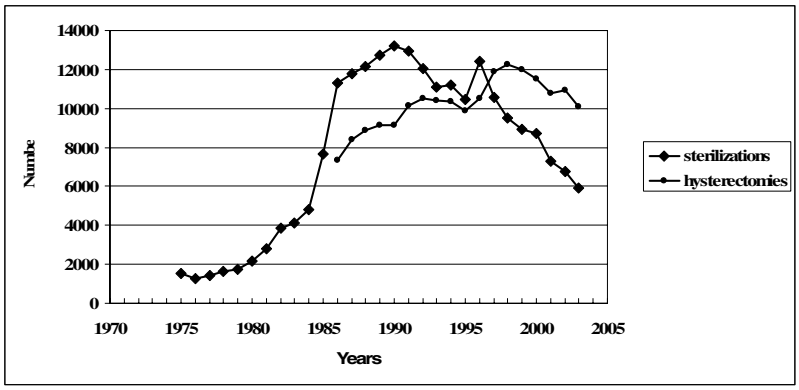


Figure 1. The annual number of registered sterilizations and hysterectomies in Finland, 1975–2003

3.2.1. Sterilization and gynecological cancers

Sterilization is a common gynecologic procedure, which appears to reduce ovarian cancer risk, but no studies on the association between sterilization and PFTC have been performed. The risk reduction concerning ovarian cancer has varied between 10 and 80% and the protective effects last for ten to twenty-five years (Table 10). There are several theories for the relationship between sterilization and ovarian cancer, including the screening effect (Weiss and Harlow 1986), a decrease in uterine growth factors that could be involved in ovarian cancer development (Riman et al. 1998), the effect of retrograde menstruation (Green et al. 1997), changes in blood flow to the ovaries (Hankinson et al. 1993) that could have an influence on plasma hormone levels and ovarian function, and blockage of exposure to ascending environmental agents, such as talc (Cramer et al. 1982). Convincing evidence that tubal ligation reduces the risk of ovarian cancer in BRCA1 mutation carriers was presented in a study by Narod et al. (Narod et al. 2001), where the OR for ovarian cancer in BRCA1 carriers with tubal ligation was 0.39 (95% CI 0.22–0.70), but in BRCA2 carriers no protective effect was seen (OR 1.19, 95% CI 0.38–3.68).

Table 10. Studies on the effect of sterilization on ovarian cancer risk

Author	Study design	Study period	Procedure	Measures of association	95%CI	Study material
Irwin et al. 1991	Case-control	1980-1982	Sterilization	Age and parity adjusted RR 0.69	0.50-0.95	494 cases, 4238 controls, 47/666 sterilizations
			Time since <4 years	0.69	0.41-1.17	
			5-9 years	0.55	0.32-0.96	
			10-14 years	0.53	0.23-1.22	
			15-19 years	1.03	0.36-2.92	
			> 20 years	1.44	0.63-3.27	
Whittemore et al. 1992	Six hospital case-control studies	1956-1988	Sterilization	Age, study, parity, OC adj. OR 0.59	0.38-0.93	2197 cases, 8893 controls 28/193 sterilizations
	Six population based case-control studies	1956-1988	Sterilization	0.87	0.62-1.2	49/566
Hankinson et al. 1993	Prospective cohort	1976-1988	Sterilization	Age-adjusted RR 0.29	0.15-0.55	Cohort of 121700 nurses, 260 cancers, 157 sterilizations
Rosenblatt et al. 1996	Multinational hospital-based case-control study	1979-1988	Sterilization	Parity and OC adjusted OR 0.71	0.47-1.08	393 cases, 2563 controls
			age < 27 years	0.92	0.46-1.84	
			age > 35 years	0.59	0.28-1.24	
			time since, 1-5 years	0.96	0.46-1.98	
			16-20 years	0.27	0.06-1.15	
			> 20 years	1.44	0.66-3.15	
Cornelison et al. 1997	Retrospective case-control	1982-1988	Sterilization	Age,parity,M,MP,OC adjusted RR 0.52	0.31-0.85	300 cases, 606 controls
Green et al. 1997	Case-control	1990-1993	Sterilization	Age, education, BMI, OC, smoking, ov.ca family history adjusted RR 0.61	0.46-0.85	824 cases, 855 controls
Kjaer et al. 2004	Population-based cohort	1977-1993	Sterilization	SIR 0.82	0.6-1.0	65232 women with sterilizations,
			Time since > 10 years	SIR 0.65	0.4-1.0	277 gynecological cancers (75 ovarian)

OC= oral contraceptive, M=menarche, MP=menopause, BMI=body mass index

The risk of other gynecological cancers after tubal sterilization still remains controversial. Endometrial cancer studies have revealed modestly increased (Rosenblatt and Thomas 1997) or decreased (Castellsague et al. 1996; Kjaer et al. 2004) risks after sterilization, or no change at all (Lacey et al. 2000). In the recent Danish study (Kjaer et al. 2004), the occurrence of cervical cancer was slightly lower and the CIN3 changes higher; findings most likely pointing to cervical screening at the time of surgery.

The risk of breast cancer after sterilization has been recently studied as part of the Nurses` Health Study. A modest protective association was observed at a time when the unipolar electrocautery method was commonly used. Unipolar electrocautery destroys more tissue than other methods and might therefore destroy blood supply of fallopian tubes and ovaries, providing some support for an association between lower lifetime exposure to hormones and a decreased risk of breast cancer (Eliassen et al. 2006). Some earlier studies revealed increased (Irwin et al. 1988), decreased (Kreiger et al. 1999; Calle et al. 2001), or unchanged (Brinton et al. 2000) risks of breast cancer.

3.3. Hysterectomy and ovarian cancer

Hysterectomy is one of the most frequent gynecological operations performed in women (Luoto et al. 1994). In 1987–1992 57,519 hysterectomies were performed in Finland (Vuorma et al. 1998) and the increase in the age-adjusted incidence rate was 12%, being 380/100,000 females in 1992. In 2003, 5892 hysterectomies were performed in Finland (Figure 1). Hysterectomy rates are slightly higher in Finland than in other Nordic countries (Luoto et al. 1994; Settnes et al. 1996). Of all women undergoing hysterectomy, 24% in 1987 and 28% in 1992 were over 50 years of age. Uterine fibroids were the most common reason for this operation in women over 45 years of age (Vuorma et al. 1998).

There are studies on the risk of ovarian cancer among women with a previous hysterectomy with or without salpingo-oophorectomy, but no studies on the risk of PFTC. Most studies have revealed a diminished risk of ovarian cancer after a previous hysterectomy (mean OR 0.57; range 0.2–0.9) and the protective effect has varied with time since hysterectomy and according to age at which the procedure had been performed (Booth et al. 1989; Irwin et al. 1991; Whittemore et al. 1992a; Hankinson et al. 1993; Green et al. 1997). The studies are shown in Table 11. The theories behind these effects mimic the theories behind the effect of sterilization.

4. SECOND PRIMARY CANCERS AFTER FIRST PRIMARY GYNECOLOGICAL CANCERS

The number of cancer survivors is rising because of earlier detection improved treatment and supportive care. In the United States the number of cancer survivors has tripled since 1971 and is growing by 2% every year (Travis 2006a). In Finland the number of new cancer cases has tripled since 1953 (Pukkala et al. 2006a). The 5-year relative survival rate among female cancer patients in Finland between 1996 and 2000 was 65%, and for males it was 56% (Pukkala et al. 2006a). In 1998, 15% of new cancer cases reported to the US SEER (Surveillance, Epidemiology, and End Results) program were second primary malignancies, and the number of second primary cancers is still increasing. Because of better survival, it has become important to validate the late effects of cancer itself and its therapy. They can be a consequence of late effects of different treatments (RT and CT) or they can reflect the effects of lifestyle (tobacco, alcohol, diet) or genetic, hormonal, immunological or environmental background of the diseases.

Secondary leukemias represented the first reported carcinogenic effects of cancer treatment (Travis 2002). Nowadays solid tumors comprise the largest proportion of second primary tumors. Therapy-associated malignancies can be divided to RT- and CT-associated tumors. Radiotherapy induces bone-marrow malignancies and solid tumors, the most sensitive organs being the breast and thyroid (Travis 2006a). Other cancers occasionally associated with radiation are those of the lung, stomach, colon, esophagus, bladder, ovary, brain and liver. The latency period of therapy-associated solid tumors is usually long, typically ten years or more (Travis 2002). The cancer type of concern in relation to CT is mainly leukemia, which is characterized by short latency. The question of the extent to which CT can induce solid tumors remains unresolved, but they have shown a dose-dependent relationship with the prior administration of cytotoxic drugs. Recent studies have shown a relationship between lung and bladder cancer after using chemotherapeutic drugs to treat Hodgkin's lymphoma (Travis et al. 1995; Travis et al. 2002) and bone sarcomas after using alkylating agents for childhood cancer (Hawkins et al. 1996).

There are many studies concerning second malignancies after first primary malignancies of the female genital system (Boice et al. 1985; Curtis et al. 1985; Storm and Ewertz 1985; Kaldor et al. 1995; Travis et al. 1996; Travis et al. 1999; Ohno et al. 2006). The risks of

Table 11. Recent studies of the association between hysterectomy and ovarian cancer

	Study design and period	Procedure	Measures of association	95%CI	Study material
Booth et al. 1989	Case-control		Age and social class		236 cases
	1978-1983	Hysterectomy	adjusted RR 0.2	0.1-0.4	451 controls
		/and unilateral			8/62 hysterectomies
		oophorectomy	0.4	0.1-1.1	2/10 hysterectomies+ unilat.oophorect.
Irwin et al. 1991	Case-control		Age and parity adjusted		
	1980-1982	Hysterectomy only	RR 0.50	0.38-0.81	494 cases
		Hysterectomy +unilateral			4238 controls
		oophorectomy	0.60	0.31-1.71	32/512 hysterectomies
					10/130 hysterectomies+ unilat.oophorect.
Whittemore et al. 1992	Six hospital case-control		Age, study, parity OC		
	studies	Any hysterectomy	adjusted OR 0.66	0.50-0.86	2197 cases, 8893 controls
	(Without s-o-ectomia)	age <40 years	0.58	0.40-0.86	85 cases, 476 controls
	1956-1986	age ≥40 years	0.73	0.51-1.0	38/ 221
					47/225
	Six population based c-c		Age, study, parity OC		
	studies	Any hysterectomy	adjusted OR 0.88	0.72-1.1	
	(Without s-o-ectomia)	age <40 years	0.76	0.57-1.0	2187 cases, 8893 controls
	1956-1986	age ≥40 years	1.0	0.77-1.3	155 cases, 789controls
Hankinson et al. 1993	Prospective cohort	Hysterectomy	Age-adjusted RR 0.66	0.45 -0.99	A cohort of 121700 nurses,
	1976-1988	age<45 years	0.51	0.23-1.15	11017 hysterectomies, 260 cancers
		age≥45 years	0.72	0.46-1.13	28 hysterectomies (220 cases)
Rosenblatt et al. 1996	Multinational hospital-		Parity and OC adjusted		393 cases, 2563 controls
	based case-control study	Hysterectomy	OR 0.41	0.14-1.21	8/84
	1979-1988	Hysterectomy+	1.06	0.34-3.29	4/27
		unilat. oophorectomy			
		age ≤40 years	0.50	1.17-1.50	4/46
		age< 40 years	0.78	0.25-2.40	4/33
Green et al.1997	Case –control study		Age, education, BMI,		
	1990-1993		OC, smoking,		
			ov.ca.family history		824 cases, 855 controls
		Hysterectomy	adjusted RR 0.64	0.48-0.85	114/171

OC=oral contraceptive, BMI= body mass index, ov.ca=ovarian cancer, unilat= unilateral

second primary cancers after these cancers are in part related to radiotherapy, in part to CT (especially leukemia and bladder cancer) and in part to genetic factors and to life-habits (smoking, HPV infections) or hormonal factors. An increased incidence of second cancers of the abdominal organs (colon, rectum, kidney, bladder, ovaries) has been observed.

In a study of second cancers after primary ovarian cancer, the standardized incidence ratio (SIR) was 1.28 for all second cancers, and significant risk increases were detected for cancers of the colon, rectum, breast, bladder and eye. For leukemia, 7- to 9-fold increases were detected (Travis et al. 1996). The overall risk was sustained with time. Following RT alone, excesses of solid tumors increased with time, being two-fold after 15+ years. For CT, the risk of solid tumors was elevated within a 5- to 9-year interval. Genetic and reproductive factors have been considered to explain the excess of breast and colorectal cancers among ovarian cancer survivors (Curtis et al. 1985; Storm and Ewertz 1985).

Second cancers after cervical cancer are mostly related to RT, and the risk remains high even 40 years after initial diagnosis. Cancers of the rectum, vagina, vulva, bladder and ovary, and leukemia, have been regarded as radiation-induced, whereas second primary cancers of the lung and bladder among cervical cancer patients have been associated with a common smoking etiology (Kleinerman et al. 1995; Ohno et al. 2006). Cervical cancer patients have been reported to experience a reduced risk of subsequent breast cancer, possibly as a result of ovarian removal or ablation by RT (Boice et al. 1985).

No studies of second primary cancers after PFTC have been performed.

5. CONCLUSIONS

Studies on PFTC are quite few and the study materials are often small. PFTC behaves similarly to ovarian cancer in many ways and it has also been treated similarly. Treatment guidelines are mostly based on studies of ovarian cancer. The etiological factors and possible risk or protective factors and prognostic factors are mostly unknown. In this study we tried to clarify these aspects.

AIMS OF THE STUDY

The present study was undertaken to investigate the occurrence of PFTC and to elucidate the risk and prognostic factors associated with it.

The specific aims of the study were:

1. to elucidate the incidence and the sociodemographic determinants of PFTC (I)

2. to investigate the effects of parity, sterilization, hysterectomy and previous cancer on the risk of PFTC (V)

3. to study specific tumor markers as prognostic factors of PFTC (II)

4. to evaluate the impact of earlier *Chlamydia trachomatis* infection on the risk of PFTC (III)

5. to evaluate the impact of earlier human papillomavirus infection on the risk of PFTC (IV)

6. to elucidate the incidence of second primary cancers after PFTC (VI)

MATERIALS AND METHODS

These studies were undertaken during 2000–2006 with the approval of the Ethics Committee of the Department of Obstetrics and Gynecology, HUCH Hospital Area, Hospital District of Helsinki and Uusimaa, and with permission of the Ministry of Health and Social Affairs.

1. STUDY MATERIAL

A summary of the study material is presented in Table 12.

Table 12. Study material

Study	*n* cases	Mean age	*n* controls	Mean age	Study period	Source of material
I	485				1953–1997	Finnish Cancer Registry linked with Population Census data
II	91	61			1985–2003	Patient registry and Serum Bank of the Department of Obstetrics and Gynecology, HUCH Hospital Area
III	79	61	156	61	1985–2000	Patient registry and Serum Bank of the Department of Obstetrics and Gynecology, HUCH Hospital Area
IV	78	62	156	64	1985–2000	Patient registry and Serum Bank of the Department of Obstetrics and Gynecology, HUCH Hospital Area
V	573		5473		1975–2004	Finnish Cancer Registry linked with HILMO and CPR
VI	2084				1943–2000	Thirteen cancer registries in Europe, Australia, Canada and Singapore
Total	3390		5785		1953–2004	

HILMO= Hospital Discharge Registry, CPR=Central Population Registry

1.1. Study I

The research on the incidence of PFTC in Finland included all patients (n = 485) who were diagnosed as having had PFTC and who were reported to the Finnish Cancer Registry in 1953–1997. More than 99% of all cancer cases have been reported to the Finnish Cancer Registry (Teppo et al. 1994). An official census of the Finnish population was organized by Statistics Finland in 1970 (Central Statistical Office of Finland, 1974). The questionnaire included information on occupation, which was coded into more than 400 occupational

categories on the basis of education, occupation, industrial status, and industry groupings (Central Statistical Office of Finland, 1974; Rauhala 1966). Four social classes were defined as follows:

I Managers and other higher administrative or clerical employees, farmers owning more than 50 hectares of land;

II Lower administrative or clerical employees, small-scale entrepreneurs, farmers owning 15–49.9 hectares of land;

III Skilled and specialized workers, farmers owning 5–14.9 hectares of land;

IV Laborers, farm and forestry workers, institution inmates, farmers owning < 5 hectares of land, retired persons whose former occupation was unknown.

The data from the Finnish Cancer Registry was linked with the Population Census data electronically using personal unique identifiers as the key. Every Finn has had a personal identification code since 1967.

1.2. Study V

All women having had PFTC in 1975–2004 were selected ($n = 573$) from the Finnish Cancer Registry. Ten age-matched (± 1 month) female controls were selected from the Finnish Central Population Registry (CPR) for each PFTC patient ($n = 5473$). The control subjects had to be alive at the time of diagnosis of the PFTC patients. The dates of birth of children of PFTC patients and control subjects were collected from the CPR. Data on sterilization, hysterectomy (Figure 1) and salpingectomy ($n = 8$) were obtained from the Hospital Discharge Registry (HILMO) which has operated since 1967 and is maintained by the National Research and Development Centre for Welfare and Health (STAKES). The Registry contains summary information on patients discharged from all public and private hospitals.

1.3. Studies II–IV

Ninety-one consecutive patients treated for PFTC at the Department of Obstetrics and Gynecology in HUCH Hospital Area during the period 1985–2000 were collected for studies II–IV. Patient data were retrieved from the records and listed on a form with 105

different sections. The patients had not received chemotherapy prior to surgery. Staging was performed according to FIGO criteria and pelvic and para-aortic lymphadenectomy was performed whenever indicated. The patients were followed up as regards recurrence and survival until February 14, 2003.

Archival serum samples stored since 1986 were used in the study. The samples were stored at -20 ^{0}C until analysis.

In study II there were 60 preoperative serum samples available, in which hCGβ, CA125 and TATI were measured. We studied the overall survival of patients with and without preoperative hCGβ data in order to exclude selection bias; the survival rates did not differ from each other. Neither did the distribution of stage, grade, tumor size, size of the residual tumor and histological type differ between the groups.

Postoperative serum samples were available from 79 PFTC patients for study III and from 78 for study IV. Control serum samples were collected from female patients from Helsinki City Maternity Hospital, operated upon because of a benign gynecological disease (91 for study III and 90 for study IV). Study III included 65 control samples which were archival serum samples from patients coming to an examination for a benign colon disease (30 controls) or which were from female employees at HUCH Hospital Area (35 controls), and study IV included 66 control archival samples (35 from female employees, 12 from patients operated upon because of benign ovarian cysts and 19 from patients seen for a benign colon disease). All controls selected fulfilled the necessary criteria: matched age at serum sampling (±5 years), and no cancer diagnosis.

1.4. Study VI

This study was a multi-center study with data from 13 different cancer registries in Finland, Denmark, Sweden, Norway, Iceland, Scotland, Spain, Slovenia, Canada (British Columbia, Manitoba and Saskatchewan), Australia and Singapore, coordinated by the International Agency for Research on Cancer (IARC). From these registries 2084 women with a first PFTC were detected. Patients for whom the first primary cancer diagnosis and death were recorded at the same time, or who had two first primary cancers recorded simultaneously were excluded (8%).

2. METHODS

2.1. Statistical analyses

2.1.1. Studies I and VI

In study I the cancer records of the Finnish Cancer Registry from 1971–1995 for persons born in 1906–1945 were linked with the census data. A total of 268 PFTC cases were found (all being a part of the total sample), for which information on social class and occupation were available from the population census. The incidence rates, age-standardized to the world population, were calculated by calendar period and urbanization level of the place of residence.

The expected numbers of cases were calculated by multiplying the stratum-specific number of person-years by the respective calendar period and birth cohort-specific incidence rate of all Finnish women. Standardized incidence ratios (SIRs) were the ratios of the observed to the expected number of cases. Confidence intervals were defined with the assumption that the observed number of cases followed a Poisson distribution.

In study VI all cases of PFTC were followed up from the date of first diagnosis (1943–2000) to the date of second primary cancer (1943–2000), date of death, date of migration or end of follow-up (1992–2000). The number of second primary cancers observed was compared with the expected number of cancers calculated from accumulated person-years and rates among females specific for each registry and five-year age and calendar-periods. The SIRs were stratified for time since PFTC diagnosis, for calendar-period of PFTC and for age at PFTC diagnosis. Poisson regression analysis was carried out as regards selected cancer sites to quantify the independent risk ratios (RRs) related to each variable.

2.1.2. Studies II–V

Analyses were performed with software packages SPSS (mostly v. 12.0), Stata 8.0 (www.stata.com) and/or Survo MM (www.survo.fi). Two-tailed *p*-values below 0.05 were considered statistically significant.

The χ^2 test was used to compare categorial variables between patients with serum marker measurements and those without (study II) and to compare differences in seropositivity of different HPV types between cases and controls (study IV). The probability of survival was

analyzed by using the Kaplan-Meier method (study II). In the analysis of overall survival, death due to any cause was defined as an event, but when analyzing disease-free survival (DFS), the event was relapse.

For evaluating prognostic factors for PFTC, univariate and multivariate Cox regression analyses were used (studies II–V).

2.2. Laboratory analyses

All serum samples were stored at -20 ^{0}C until analyzed. Serum samples for the analyses in study II were preoperatively collected and in studies III and IV they were collected postoperatively. The assays are summarized in Table 13 and presented in detail in the original articles.

Table 13. Characteristics of assays used for laboratory analyses.

Factor	Principle of assay	Source of reagents
hCGβ	Fluoroimmunoassay	In-house method[1]
CA125	Immunol1® Immunoanalyzer Immunoradiometric assay	Bayer, Tarrytown, N.Y., USA
TATI	Radioimmunoassay	Orion Diagnostica, Espoo, Finland
C. trachomatis IgG	Micro-immunofluorescence (MIF)	Washington Research Foundation, Seattle, WA, United States
	peptide EIA	ANILabsystems, Helsinki, Finland
C. pneumoniae IgG	MIF	Washington Research Foundation, Seattle, WA, United States
HPV IgG	EIA using VLP capsid protein as antigen	HVP16: Lab.of Cellular Oncology, NCI, NIH, Bethesda, USA; HPV6 and 11: Merck Research Laboratories, West Point, PA, USA; HPV31 and 33: Vienna Medical School, Austria; HPV18: GlaxoSmithKline Biologicals in Rixensart, Belgium
HSV-2 IgG	EIA	EIA, Biokit SA, Spain

[1]Alfthan et al. 1988, *C. trachomatis* = *Chlamydia trachomatis*
EIA= enzyme immunoassay
VLP= virus-like particle

RESULTS

The main results are summarized in Table 14 and presented in the text; details are given in the separate original publications.

Table 14. Summary of the results of the study on PFTC.

Factor	Protective effect	Risk factor	Other results
Social class			Incidence higher in upper social classes
Urban/rural areas in Finland			Incidence higher in the cities, relative rise higher in rural areas
Occupation			Incidence higher among nurses, private secretaries, hairdressers and barbers, book-keepers and accountants
Parity	++		Protection higher with increasing number of deliveries
Previous sterilization	+		
Previous hysterectomy	-	-	
Serum hCGβ		A high value is a marker of worsened prognosis	
Chlamydia trachomatis	-	-	
Human papillomavirus	-	-	
Second primary cancers			SIR* for second primary cancers 1.4 (95% CI 1.1–1.6), especially to breast, colorectal, bladder, lung cancer and NLL

*SIR= standardized incidence ratio, NLL= non-lymphoid leukemia

1. INCIDENCE AND SOCIODEMOGRAPHIC DETERMINANTS OF PFTC (I)

The incidence of PFTC increased during the study period. It was highest among upper social classes and in the cities.

The age-adjusted incidence of PFTC in Finland increased from 1.2/1,000,000 in 1953–57 to 5.4/1,000,000 in 1993–1997, indicating a 4.5-fold increase corresponding to a 7-fold increase in the absolute number of new cases. In 1993–1997 108 new cases of PFTC were registered at the Finnish Cancer Registry.

The incidence was most pronounced in the oldest age groups. During 1953–67 the peak incidence was observed in the age group 50–54 years, whereas during 1983–97 the incidence was highest between 60 and 64 years of age. In rural areas, the incidence was lower, but the relative increase was higher than in the cities (Figure 2).

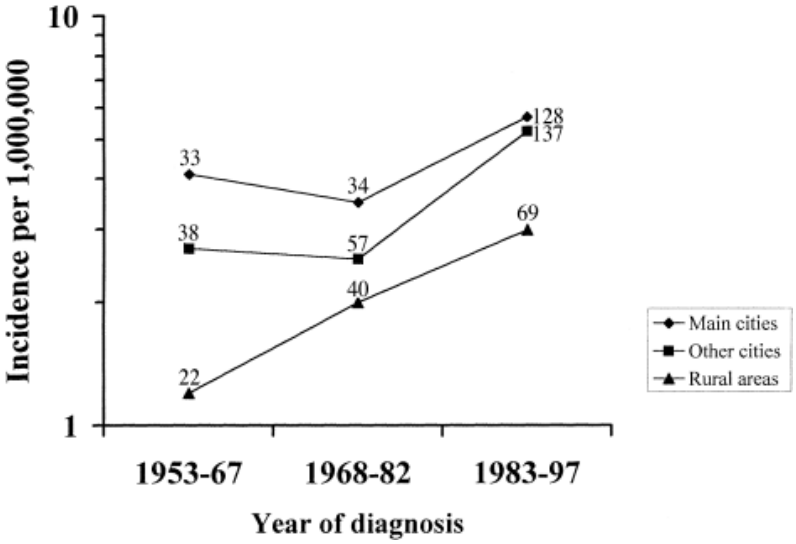


Figure 2. Incidence rates per 1,000,000 of primary fallopian tube cancer in different areas in Finland expressed in 15-year periods from 1953–97, adjusted for age to the world standard population. Main cities: Helsinki, Tampere, Turku. Numbers of cases in each category are shown.

There were 268 PFTC cases diagnosed in 1971–1995 among women born in 1906–45, for which information on social class and occupation were available from the Population Census of 1970. The SIRs increased toward higher social classes (results shown in Table 15).

Table 15. Number of women born between 1906 and 1945 in the cohort in 1970; and observed and expected numbers and standardized incidence ratios (SIRs) of primary fallopian tube carcinomas observed during 1971-1995 among women, by social class.

Social class	Observed	Expected	SIR (95% CI)[2]	Women in Cohort (*n*)
I	25	20	1.27 (0.81-1.87)	88 737
II	95	74	1.28 (1.04-1.57)	405 654
III	114	128	0.89 (0.74-1.06)	595 805
IV	34	46	0.73 (0.51-1.02)	177 474
Total	268	268	1.00 (Reference)	1 267 670

The incidence was high in various occupations in health care, technical, physical and social science, humanistic and artistic work as well as in administrative and clerical work. In specific occupations, increased risks of PFTC were observed among private secretaries (SIR 4.4, 95% CI 1.4–10), nurses (SIR 4.0, 95% CI 2.1–7.0), hairdressers and barbers (SIR 3.9, 95% CI 1.3–9.2), and bookkeepers and accountants (SIR 3.6, 95% CI 1.6–7.1). In contrast, low SIRs were observed among women in farming, fishing and forestry work as well as among economically inactive women (Table 16).

Table 16. Observed number of cases and standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) for PFTC in the main occupational categories from 1971 through 1995,among women born from 1906 through 1945.

Occupation	Observed	SIR (95%CI)
"Academic" work*	37	1.63 (1.15-2.25)
Administrative and clerical work	35	1.60 (1.12-2.23)
All economically active persons	180	1.11 (0.96-1.28)
Transport and communications	6	1.09 (0.40-2.37)
Whole population	268	1.00 (0.88-1.12)
Services	32	1.00 (0.69-1.42)
Sales professions	16	0.98 (0.56-1.59)
Industrial and construction work	27	0.95 (0.63-1.38)
Economically inactive**	88	0.83 (0.66-1.02)
Farming, forestry and fishing	27	0.79 (0.52-1.14)

*Technical, physical science, social science, humanistic, and artistic work. ** >50% housewives

2. EFFECTS OF PARITY, STERILIZATION, HYSTERECTOMY AND A PREVIOUS CANCER (V)

Parity gave the strongest protection against PFTC and the protection got stronger by number of deliveries, whereas a previous sterilization procedure gave a mild protection. A previous hysterectomy did not give any protection.

Parity

In univariate analysis the OR for parity was 0.54 (95% CI 0.39–0.75) when compared with nulliparous women. The older age (≥ 35 years) at first birth was also protective (Table 17). In multivariate analysis, parity was the only significant protective factor. The protective effect increased with increasing number of deliveries: OR for 1–2 deliveries 0.63, 95% CI 0.44–0.91; and for ≥ 3 deliveries 0.32, 95% CI 0.19–0.52 (Table 18).

Sterilization, hysterectomy and a previous cancer

In univariate analysis the protective effect of a previous sterilization was of borderline significance (OR 0.58, 95% CI 0.33–1.00) and the effect increased among those who were ≤ 40 years at the time of sterilization (OR 0.30, 95% CI 0.11-0.84) and a longer time since the procedure also gave protection (OR 0.29, 95% CI 0.11-0.79). The OR for an earlier hysterectomy in univariate analysis was 1.14 (95% CI 0.66-1.98). A previous cancer was a significant risk factor for PFTC (OR 1.69, 95% CI 1.08–2.67), especially a previous breast cancer (OR 1.69, 95% CI 1.08–2.67) (Table 17).

In multivariate analysis sterilization did not reduce significantly the risk of PFTC (OR 0.74, 95% CI 0.42–1.30). PFTC patients had undergone hysterectomy more often than the controls (OR 1.27, 95% CI 0.73–2.21). Previous breast cancer increased the risk, but non-significantly (OR 1.63, 95% CI 0.70–3.77) (Table 18).

3. TUMOR MARKERS AS PROGNOSTIC FACTORS OF PFTC (II)

Twenty-three percent of the patients presented stage I-II disease. Eighty percent of the carcinomas were of serous type. Preoperative serum concentrations of hCGβ, CA125 and TATI were elevated in 37%, 90% and 20% of the cases, respectively. In survival analysis, the overall and disease-free 5-year survival rate was 33%. When analyzing disease-free 5-year survival rates, the most important prognostic factors were size of the residual tumor

Table 17. Univariate analysis of anamnestic factors associated with PFTC.

	Cases		Controls		OR	95% CI
	n	(%)	*n*	(%)		
All women	565		5473			
No previous cancer	519	(91.9)	5151	(94.1)	1.00	Reference
Previous cancer	46	(8.1)	322	(5.9)	1.42	1.03 - 1.98
Type of previous cancer						
No previous cancer	519		5151		1.00	Reference
Breast cancer	23		135		1.69	1.08 - 2.67
Other cancer	23		187		1.23	0.79 - 1.91
Women born 1925+	375		3587			
No sterilization	360	(96.0)	3357	(93.6)	1.00	Reference
Sterilization	15	(4.0)	230	(6.4)	0.58	0.33 - 1.00
Age at sterilization						
No sterilization	360		3357		1.00	Reference
< 40 years	4		115		0.30	0.11 - 0.84
≥ 40 years	11		115		0.85	0.45 - 1.61
Time since sterilization						
No sterilization	360		3357		1.00	Reference
< 10 years	11		108		0.93	0.48 - 1.81
≥ 10 years	4		122		0.29	0.11 - 0.79
Women born 1936+	189		1764			
No hysterectomy	173	(91.5)	1633	(92.6)	1.00	Reference
Hysterectomy	16	(8.5)	131	(7.4)	1.14	0.66 - 1.98
Age at hysterectomy						
No hysterectomy	173		1633		1.00	Reference
< 45 years	9		63		1.36	0.66 - 2.79
≥ 45 years	7		68		0.95	0.42 - 2.12
Time since hysterectomy						
No hysterectomy	173		1633		1.00	Reference
< 10 years	9		102		0.84	0.41 - 1.69
≥ 10 years	7		29		2.19	0.93 - 5.16
No deliveries	51	(27.0)	280	(15.9)	1.00	Reference
Women with deliveries	138	(73.0)	1484	(84.1)	0.54	0.39 - 0.75
Age at first birth						
No deliveries	51		280		1.00	Reference
< 35 years	135		1428		0.52	0.37 - 0.74
≥ 35 years	3		56		0.30	0.09 - 1.00
Parity						
No deliveries	51		280		1.00	Reference
1-2 deliveries	111		994		0.62	0.44 - 0.89
3 or more deliveries	27		490		0.30	0.18 - 0.49

CI = confidence Interval OR = odds ratios

Table 18. Odds Ratios (ORs) in multivariate analysis of factors associated with PFTC (189 cases, 1764 controls).

	Cases, *n*	Controls, *n*	OR	95% CI
Parity				
No deliveries	51	280	1.00	Reference
1-2 deliveries	111	994	0.63	0.44-0.91
3 or more deliveries	27	490	0.32	0.19-0.52
No sterilization	174	1539	1.00	Reference
Sterilization	15	225	0.74	0.42-1.30
No hysterectomy	173	1633	1.00	Reference
Hysterectomy	16	131	1.27	0.73-2.21
No previous breast cancer	182	1727	1.00	Reference
Previous breast cancer	7	37	1.63	0.70-3.77

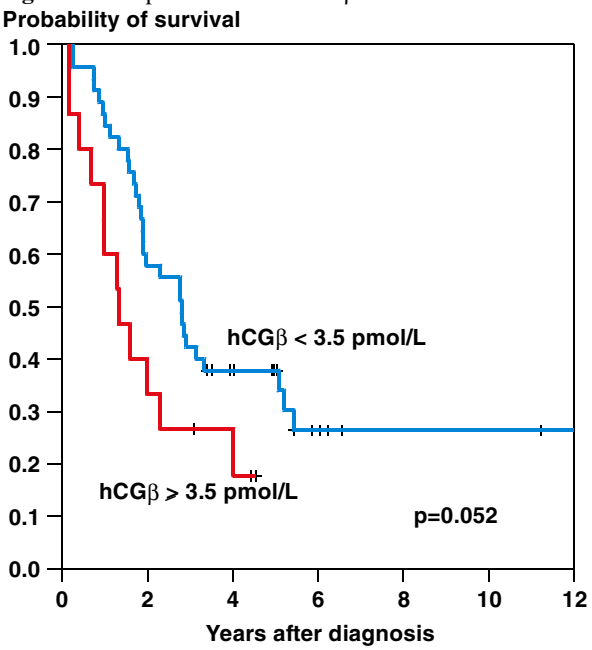
CI = confidence interval

($p = 0.013$) and stage ($p = 0.014$). Size of the residual tumor strongly influenced overall 5-year survival, the survival rate for patients with residual tumor of < 1 cm being 51%, compared with only 20% among patients with residual tumor of ≥ 1 cm ($p = 0.003$). In patients with serous carcinoma, the overall 5-year survival rate was 37%, compared with 17% in those with other tumor types ($p = 0.023$).

When studying tumor markers as prognostic factors and in survival analyses, we used the 75th percentile for all markers. The overall 5-year survival rate was 38% when serum hCGβ concentrations were below the 75th percentile (< 3.5 pmol/L) and 18% when it was higher ($p = 0.052$) (Figure 3), disease-free survival rates being 38% and 20%, respectively ($p = 0.014$).

We also evaluated the prognostic value of the tumor markers CA125 and TATI. High levels of CA125 (above the 75th percentile [1017 kU/L]) predicted shorter survival times compared with serum levels below that, the overall 5-year survival rates being 14% and 39%, respectively ($p = 0.009$). Disease-free 5-year survival rates were not significantly different. Elevated serum TATI values were sparse and were not of prognostic significance as regards survival.

Figure 3. Preoperative serum hCGβ concentrations and overall survival of PFTC patients (n = 60).



In univariate analysis serum hCGβ concentration (p = 0.019), stage III–IV disease (p = 0.020), stage IV disease (p = 0.025) and size of the residual tumor (p = 0.019) were all associated with DFS, while the size of the residual tumor (≤ 1 cm) (p = 0.004), serum CA125 > 1017 kU/L (p = 0.012) and stage IV (p = 0.018) were significantly associated with OS. When all the variables were fitted as multiple variables in the same model, only hCGβ (RR 2.80, p = 0.043) and the histology of the tumor (RR 3.17, p = 0.013) were independent prognostic factors for OS and only hCGβ was an independent prognostic factor for DFS (RR 3.07, p = 0.041). In a backward stepwise model, hCGβ (RR 2.49, p = 0.012), stage IV (RR 2.47, p = 0.012) and histology (RR 2.71, p = 0.010) emerged as independent prognostic factors (Table 19).

Table 19. Significance of prognostic factors when fitted in Cox backward stepwise regression model as multiple variables¤.

Overall survival

Factor	RR*	95% CI	p-value
Histology	2.71	1.26-5.83	0.010
Stage IV	2.47	1.21-5.02	0.012
hCGβ>3.5pmol/L	2.49	1.22-5.09	0.012

*Risk ratio

¤Variables included in the model: grade, S-CA125, S-TATI, age, size of the residual tumor.

4. IMPACT OF PAST CHLAMYDIAL INFECTION ON THE RISK OF PFTC (III)

The effect of a past chlamydial infection was studied in a retrospective serologic case-control study. The study did not reveal any risk effect of a previous chlamydial infection on PFTC. A summary of the characteristics of PFTC patients is shown in Table 20.

Table 20.Clinical characteristics of the PFTC patients in study III

Parameter	*n*	(%)
Stage		
I	11	(14)
II	12	(15)
III	40	(51)
IV	15	(19)
No data	1	(1)
Grade		
1	7	(9)
2	20	(25)
3	45	(57)
No data	7	(9)
Histological type		
Serous	57	(72)
Anaplastic	13	(16)
Carcinosarcoma	5	(7)
Endometrioid	1	(1)
Clear cell	1	(1)
Unknown	2	(3)
Tumor size (cm)		
<2	7	(9)
2 - 5	14	(18)
5 -10	19	(24)
>10	36	(45)
No data	3	(4)
Residual tumor size (cm)		
None	28	(35)
<0.5	2	(3)
0.5 - 1.0	1	(1)
1 - 2	4	(5)
>2	30	(38)
Peritoneal carcinosis	10	(13)
No data	4	(5)

n = Number of patients

Seropositivity to different *Chlamydia trachomatis* serovars and to *C. pneumoniae* did not differ between patients and controls, seropositivity varying from 13.9% to 21.5% in PFTC patients and from 10.3% to 21.8% in control subjects. The overall prevalence of CTR IgG antibodies to one or more serotype pools in PFTC patients and controls was 20% and 16%, respectively ($p = 0.42$). When analyzing the relationship between CTR or *C. pneumoniae* IgG antibodies versus PFTC, no association was detected (Table 21). The presence of serum IgG antibodies to more than one serotype pool did not increase the risk of PFTC (Table 22).

Table 21. Odds ratios calculated by conditional logistic regression analysis of PFTC associated with different *C. trachomatis* serovars and with *C. pneumoniae*

	OR	**95% CI***
C.trachomatis serotype pools		
CHIJ	1.6	0.7–3.5
BED	1.4	0.6–3.2
GFK	1.1	0.5–2.4
C.pneumoniae	1.0	0.5–1.9

* CI = confidence interval

Table 22. Risk of PFTC by number of positive *C.trachomatis* serotype pools in PFTC patients and controls: univariate analysis

	CTR- positive				
Number of serotype pools	**Cases *n* (%)**	**Controls *n* (%)**	**OR***	**95%CI****	**p-value**
0	63 (80)	131 (84)	1.0		
1	3 (4)	5 (3)	1.2	0.3–5.4	0.7
2	5 (6)	9 (6)	1.1	0.4–3.6	0.8
3	8 (10)	11 (7)	1.5	0.6–3.9	0.4
Total	79 (100)	156 (100)			

*OR= odds ratio, **CI= confidence interval

5. THE IMPACT OF HPV INFECTION ON THE RISK OF PFTC (IV)

In our study none of the seroprevalences of different HPV types differed between PFTC patients and controls (Table 23), nor did the rates of seropositivity to more than one HPV type differ between cases and controls.

Table 23. Seropositivity to different HPV types, *C.trachomatis* and HSV-2 in 78 PFTC patients and 156 controls

	Cases *n* (%)	**Controls *n* (%)**	p-value
HPV			
HPV6	8 (10)	15 (10)	0.88
HPV11	10 (13)	17 (11)	0.66
HPV16	17 (22)	33 (21)	0.91
HPV18	5 (6)	8 (5)	0.69
HPV31	11 (14)	21 (13)	0.89
HPV33	8 (10)	17 (11)	0.88
C. trachomatis	14 (18)	28 (18)	0.90
HSV-2	19 (24)	34 (22)	0.60

To study the possible effect of a papillomavirus infection with more than one HPV type, we analyzed seropositivity to one or more HPV types. Seropositivity to multiple HPV types did not increase the risk of PFTC (Table 24). All HPV-specific risk estimates of PFTC were non-significant.

Table 24. Adjusted odds ratios of PFTC by seropositivity to high- low-risk HPV types

Seropositivity to one or more of HPV 16/18/31/33	Seropositivity to HPV6/11	Number of Cases	Controls	OR	(95% CI)☼
0	No	47	91	1.00	(reference)
0	Yes	5	12	0.80	(0.27–2.42)
1	No	14	28	0.96	(0.40–2.02)
1	Yes	2	7	0.57	(0.11–2.85)
2 to 4	No	6	13	0.88	(0.32–2.46)
2 to 4	Yes	4	5	1.44	(0.37–5.61)

☼Adjusted for seropositivity to herpes simplex virus type 2 and *C. trachomatis*

6. SECOND PRIMARY CANCERS AFTER PFTC (VI)

The time since PFTC was an important factor when analyzing the risk of second primary cancers. There were 118 cancer cases observed after 2084 previous cases of PFTC (SIR 1.4, 95% CI 1.1–1.6). Elevated SIRs were seen for non-lymphoid leukemia (3.7, 95% CI 1.0–9.4), bladder (2.8, 95% CI 1.0–6.0), lung (1.8, 95% CI 0.9–3.2), colorectal (1.7, 95% CI 1.0–2.6) and breast cancer (1.5, 95% CI 1.1–2.2) (Table 25). The SIR for a second cancer (all sites combined) was highest if the time since PFTC diagnosis was 10+ years, age at PFTC diagnosis < 60 years, or the year of PFTC diagnosis was before 1984 (Table 26).

For breast cancer, a significantly elevated SIR of 2.3 (95% CI 1.2–3.8) was seen at more than 10 years after the diagnosis of PFTC. In multivariate analysis also, there was an indication of an increase of breast cancer cases 10+ years after PFTC, compared with shorter follow-up times.

For colorectal cancer, a significant increase (SIR 2.1, 95% CI 1.3–4.9) was detected during the second to fifth year after PFTC diagnosis (Table 26). If PFTC was diagnosed before the age of 60 years, the RR of colorectal cancer tended to be high (combined SIR of age categories < 50 and 50–59 years 2.2; 95% CI 1.1–4.0). Multivariate analysis gave essentially the same result: RR 1–4 years after PFTC was 3.3 compared with follow-up of 10+ years (95% CI 1.0–11) and RR related to PFTC diagnosed at ages 60+ years or in 1991+ compared with younger ages or earlier calendar periods was also lower.

In multivariate analysis concerning the remaining cancers combined (after exclusion of breast and colorectal cancers) there was some indication of a higher risk related to PFTC diagnoses before 1984. Elevated risks after PFTC were also detected for non-lymphoid leukemia during the second to tenth year after PFTC diagnosis (four cases, SIR 6.9, 95% CI 1.9–17.8) and for bladder cancer in follow-up at 5+ years (seven cases, SIR 4.2, 95% CI 1.4–9.7)

Table 25. Observed numbers of subsequent primary cancer cases after PFTC among 2084 women. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) are shown.

Cancer site (ICD-9)	Observed	SIR	95 % CI
All malignant (140-208)	118	**1.4**	1.1 - 1.6
Oral cavity, pharynx (140-149)	2	**1.5**	0.2 - 5.6
Esophagus (150)	1	**1.3**	0.0 - 7.3
Stomach (151)	3	**0.7**	0.2 - 2.2
Small intestine (152)	1	**3.5**	0.1 - 20
Colorectal (153,154)	20	**1.7**	1.0 - 2.6
Colon (153)	13	**1.7**	0.9 - 2.9
Rectum (154)	7	**1.7**	0.7 - 3.5
Liver (155.0,155.1)	0	-	0.0 - 5.0
Gall bladder, bile ducts (156)	3	**1.9**	0.4 - 5.5
Pancreas (157)	4	**1.3**	0.4 - 3.3
Peritoneum (158)	0	**-**	0.0 - 28
Lung (162)	11	**1.8**	0.9 - 3.2
Bone (170)	0	**-**	0.0 - 34
Soft tissue sarcoma (171)	1	**2.5**	0.1 - 14
Melanoma of skin (172)	1	**0.4**	0.0 - 2.5
Other neoplasm of skin (173)	9	**1.5**	0.7 - 2.9
Breast (174)	33	**1.5**	1.1 - 2.2
Cervix uteri (180)	2	**0.7**	0.1 - 2.4
Corpus uteri (182)	2	**0.3**	0.0 - 1.3
Other female genital (179,184)	2	**1.8**	0.2 - 6.7
Bladder (188,189.3-4)	6	**2.8**	1.0 - 6.0
Kidney (189.0-2,189.5-9)	2	**0.9**	0.1 - 3.1
Brain, nervous system (191-192)	0	**-**	0.0 - 3.3
Thyroid gland (193)	2	**2.3**	0.3 - 8.3
Hodgkin's disease (201)	0	**-**	0.0 - 15
Non-Hodgkin's lymphoma (200,202)	2	**0.9**	0.1 - 3.1
Multiple myeloma (203)	1	**0.8**	0.0 - 4.4
Leukemia (204-208)	5	**2.6**	0.8 - 6.0
Lymphoid (204)	1	**1.2**	0.0 - 6.5
Non-lymphoid (205-208)	4	**3.7**	1.0 - 9.4
Others	5	**1.2**	0.4 - 2.7

Table 26. Observed numbers (Obs) and standardized incidence ratios (SIRs) for second primary cancer among 2084 women with an earlier first PFTC, by age and calendar period at PFTC diagnosis and by time since PFTC diagnosis.

	Cancer site (ICD-9)								
Factor	**All malignant** (140-208)			**Female breast** (174)			**Colorectal** (153,154)		
	Obs	**SIR**	95% CI	Obs	**SIR**	95% CI	Obs	**SIR**	95% CI
Age at PFTC diagnosis									
<50	26	**1.6**	1.0-2.4	7	**1.4**	0.6-2.8	4	**2.3**	0.6-5.9
50-59	39	**1.5**	1.1-2.1	12	**1.8**	0.9-3.0	7	**2.2**	0.9-4.5
>60	53	**1.2**	0.9-1.6	14	**1.4**	0.8-2.4	9	**1.3**	0.6-2.5
Calendar period of PFTC diagnosis									
<1975	46	**1.5**	1.1-2.0	11	**1.6**	0.8-2.9	8	**1.8**	0.8-3.6
1975-1983	31	**1.5**	1.0-2.1	9	**1.8**	0.8-3.4	5	**1.7**	0.6-4.0
1984-1990	24	**1.2**	0.8-1.8	7	**1.3**	0.5-2.7	5	**2.0**	0.6-4.6
1991+	17	**1.1**	0.6-1.7	6	**1.3**	0.5 -2.9	2	**1.0**	0.1-3.5
Time since PFTC diagnosis (years)									
<1	15	**1.2**	0.7-2.0	5	**1.5**	0.5-3.4	2	**1.2**	0.2-4.4
1-4	42	**1.5**	1.1-2.0	9	**1.2**	0.5-2.3	10	**2.7**	1.3-4.9
5-9	17	**1.0**	0.6-1.5	5	**1.1**	0.4-2.6	2	**0.8**	0.1-3.0
10+	44	**1.6**	1.2-2.2	14	**2.3**	1.2-3.8	6	**1.5**	0.5-3.2

DISCUSSION

Less than 2500 cases of PFTC have been described worldwide. A commonly occurring problem is how to differentiate PFTC from ovarian carcinoma. The WHO has classified these tumors as follows: a malignant epithelial tumor of the fallopian tube must be located macroscopically within the tube or its fimbriated end, and the uterus and ovary must either not contain carcinoma or, if they do, it must be clearly different from the fallopian tube lesion. Malignant epithelial ovarian tumors originate from the ovarian surface epithelium or its derivates (Tavassoli et al. 2003). Ovarian and fallopian carcinomas behave similarly in many ways and they are treated under similar guidelines.

Epidemiology is the study of diseases in populations of humans, specifically how, when and where they occur. Epidemiological research is aimed at determining what factors are associated with diseases (risk factors), and what factors may protect people against disease (protective factors). Epidemiological studies can show that a risk factor is associated (correlated) with a higher incidence of disease in the population exposed to that risk factor.

One of the major aspects in the present study was to elucidate the occurrence of PFTC in Finland and to study possible risk factors, such as previous *Chlamydia trachomatis* infection or HPV infection. Possible protective factors such as parity, previous sterilization and hysterectomy were also studied. As prognostic factors of PFTC (factors that can be used to estimate recovery and survival), serum tumor markers were studied. We also wanted to clarify the behavior of this disease by exploring its tendency to express hCGβ.

Risk and protective factors have different biological mechanisms through which they finally affect the development of cancer. They can promote tumorigenesis by inducing genomic changes. They can affect cytokinetics, e.g. by inhibiting apoptosis or by promoting angiogenesis.

The incidence of PFTC (I)

Incidence refers to the number of new cases developing during some specific time interval. The incidence of PFTC was clarified using Finnish Cancer Registry and Population Census data. The age-adjusted incidence increased more than 4-fold during the whole study period, being 5.4/1,000,000 at the end and it was highest in the oldest age groups, as is

understandable because of the change in population structure: in 1950 6.7% of the Finnish population was over 65 years of age, compared with 15.6% in 2003 (Statistics Finland, demographic statistics). The projected figure for the population over 65 years of age in 2040 will be 27%, which could indicate a rapid rise in the incidence of PFTC. There are only two other studies reporting the incidence of PFTC, the SEER program rates in the United States (3.3/1,000,000 among Caucasian women) being lower than our respective rates (National Cancer Institute 2001). The rates in Denmark (2.9/1,000,000) resemble our rates around 1980 (Pfeiffer et al. 1989). The peak incidence occurred between the ages of 60–64 years, whereas in the United States, the peak incidence has been highest between the ages of 70–74 years.

In our study the incidence of PFTC was highest in the main cities, but the relative rise was higher in rural areas than in the cities, perhaps reflecting the adoption of urban lifestyle factors in rural areas. Part of the variation between these areas could be explained by changes in parity. The lower incidence rates in rural areas and among workers in the fields of farming, forestry and fishing could reflect the influence of environmental and lifestyle factors in the etiology of PFTC. It may also reflect differences in availability of health care services between rural and urban areas. The differences in incidence among women in different occupations are difficult to explain, but part of the variation may be explained by real occupational exposures.

The incidence rate of PFTC was greatest in higher social classes, as is also the case among breast and endometrial cancer patients, but not as clearly among ovarian cancer patients in Finland (Pukkala 1995; Robert et al. 2004). This may reflect the effect of lower parity in higher social classes.

A proportion of the rise in incidence may be explained by better diagnostic criteria as regards PFTC and attentiveness of pathologists in classifying between ovarian cancer and PFTC even when only small biopsies are available. In our studies, a large proportion of the PFTC patients had stage III disease, a situation that differs from that in many earlier studies (Peters et al. 1988, Hellström et al. 1994, Baekelandt et al. 2000). This may reflect the attentiveness of our pathologists in differential diagnostics between ovarian cancer and PFTC, even in later stages. The rise of incidence of PFTC in Finland goes in line with the rise of incidence in ovarian cancer, the rise of latter being much lower though (Figure 4).

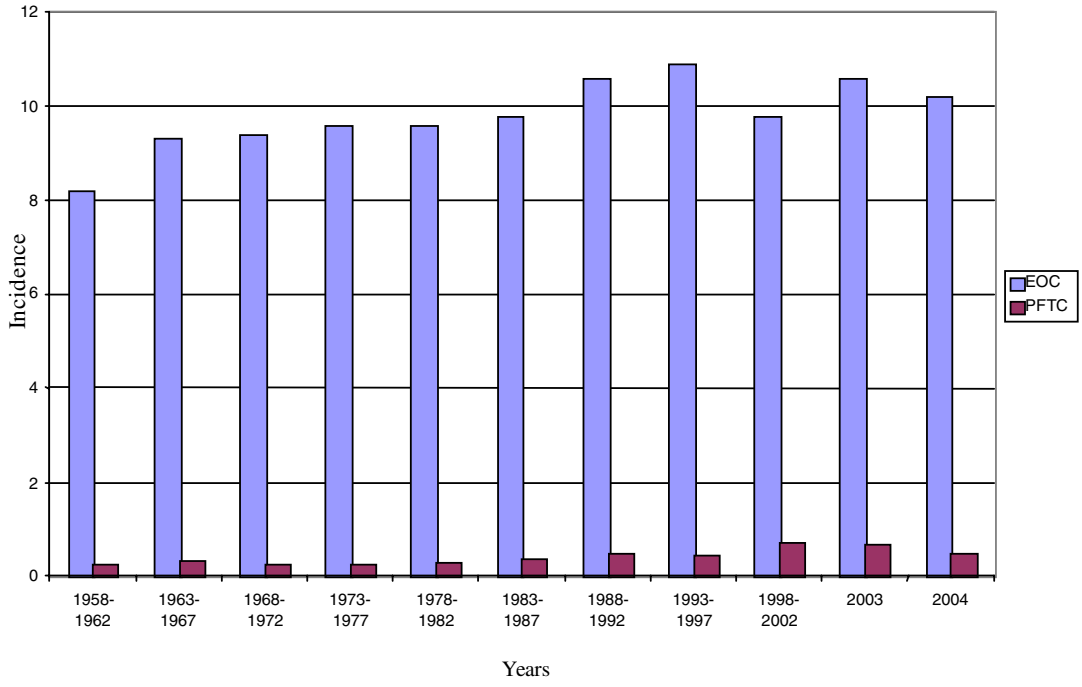


Figure 4. The incidence rates of PFTC and epithelial ovarian cancer (EOC) in Finland, 1958–2004 (Finnish Cancer Registry). Incidence rates / 100,000

In conclusion, the incidence rate increased in Finland during the follow-up years. The incidence rates were highest among higher social classes, in some occupations and in the main cities, perhaps reflecting in part an effect of occupational exposure, in part an effect of lifestyle habits and in part an effect of parity. The results may predict ever increasing incidence rates, as the levels of higher social classes today seem to predict the average level in the whole population in the future (Pukkala 1995).

Parity, sterilization and hysterectomy as protective factors as regards PFTC (V)

The present study clearly indicates the protective effect of parity on the risk of PFTC. There are no earlier studies in which the effect of parity on the risk of PFTC has been evaluated, but the present findings correlate with the results of studies on ovarian cancer. Ovarian and tubal carcinomas share many features. In organogenesis they both develop from the Müllerian duct and are histologically nearly identical; hence it is logical to compare the results with those of studies on ovarian cancer. Several studies on ovarian cancer have revealed a similar protective effect of parity (Whittemore et al. 1992a; Adami et al. 1994;

Risch et al. 1994; Albrektsen et al. 1996; Riman et al. 1998), the most recent study being from Finland (Hinkula et al. 2006). In a large analysis in the U.S. a 40% reduction in the risk of ovarian cancer was found as regards first full-term pregnancy and each birth after the first incurred another 14% decrease (Whittemore et al. 1992a). In the study carried out by Hinkula et al. an increase from five to eight births did not increase the protection against ovarian cancer (Hinkula et al. 2006). Earlier studies have revealed varying results concerning the age at first or last birth on the risk of ovarian cancer. Some studies have revealed an increased risk of ovarian cancer at an older age at first birth (Booth et al. 1989), and some a decreased risk (Whittemore et al. 1992a; Purdie et al. 1995; Cooper et al. 1999; Titus-Ernstoff et al. 2001). Some revealed no association between the age at first birth and ovarian cancer (Risch et al. 1994; Hankinson et al. 1995). In the present study, older age at first birth gave more protection against PFTC than age of < 35 years at first birth and the protective effect of deliveries became stronger with increasing number of deliveries.

There are several theories concerned with trying to explain the influence of age at first birth on the risk of ovarian cancer. The hypotheses are largely based on the gonadotropin hypothesis and on the incessant ovulation hypothesis. Pituitary secretion of gonadotropins generally increases during adulthood, but decreases during pregnancy. The protective effects of later childbirth are consistent with the gonadotropin hypothesis. Adami et al. suggested a theory based on pregnancy-dependent clearance from the ovaries of cells that have undergone malignant transformation (Adami et al. 1994). One possible explanation for the reducing effect of pregnancy on the risk of ovarian cancer could be the high levels of progesterone during pregnancy that induce apoptosis of transformed epithelial cells (Rodriguez et al. 1998). We have to keep in mind that all these studies concern ovarian cancer, but because the endothelial lining of the fallopian tube is hormonally reactive, both cancers could behave in a similar way, even though in the fallopian tube there is no ovulation trauma.

In the current study we found a reduced risk of PFTC after sterilization in univariate analysis. The effect became stronger with time since the procedure and with younger age of the patients at the time of the operation. There are no earlier studies on the effect of sterilization on the risk of PFTC. Our results are in accordance with those of most studies conducted concerning ovarian cancer (Table 10). However, in the present study, in multivariate analysis the protective effect did not reach statistical significance.

In our study sterilizations occurring more than half a year before the PFTC diagnoses (or the corresponding day for controls) were included to obtain reliable data on the effect of previous sterilization on the risk of PFTC. In addition, we excluded women with an operation code for unilateral or bilateral salpingectomy before the day of PFTC diagnosis. Reliable data on sterilizations were available from 1975. We included women born after 1925 in sterilization analyses, assuming that a sterilization procedure is no longer necessary for women aged 50 years or more. With these criteria, the reliability of our data is good and the analysis appropriate. Our data were not adjusted for menarche, menopause or use of oral contraceptives, all of them being possible confounding factors.

In the present study hysterectomy did not give any protection against PFTC. On the contrary, it was a risk factor (though insignificant) in univariate analysis, showing increasing risk with time since operation and with younger age at operation. We cannot explain this result, but the study material was small concerning previous hysterectomy ($n = 16$). To verify this finding, future research is needed with a larger amount of material. Hysterectomy data were available from 1986 and only events occurring more than half a year before the diagnosis of PFTC were used. In addition, only women born after 1936 were included to ensure that all hysterectomies during the analysis period would have been registered. The absence of the same confounding factors as for analyses concerning sterilization was also a limitation of this analysis.

Our study also involved analysis of the effect of a previous cancer on the risk of PFTC. The cancer cases were collected from the Finnish Cancer Registry and linked with CPR data. In univariate analysis, a previous cancer, especially breast cancer, was a risk factor of PFTC, but the data were not significant in multivariate analysis. Previous studies indicate that BRCA1 and BRCA2 mutations are more common among PFTC patients than in the normal population (Aziz et al. 2001; Cass et al. 2005). On the other hand, protective factors such as the long-term protective effect of parity on breast cancer risk and PFTC risk may be similar (Ewertz et al. 1990; Hinkula et al. 2001).

In conclusion, parity is a clearly protective factor as regards PFTC, showing an increasing effect with increasing number of deliveries, perhaps reflecting a hormonal background for the disease. Further studies are needed to resolve the mechanism behind this association.

Serum hCGβ as a prognostic factor of PFTC (II)

In serum, hCGβ concentrations are elevated in many non-trophoblastic malignancies (Alfthan et al. 1992; Carter et al. 1994; Carter et al. 1995; Gillott et al. 1996; Vartiainen et al. 2001; Hotakainen et al. 2002; Louhimo et al. 2002; Louhimo et al. 2004a; Louhimo et al. 2004b) and also in some trophoblastic diseases (Stenman et al. 1985). Low levels of hCG and hCGβ are also expressed in many benign pancreatic, colorectal and gastric diseases (Alfthan et al. 1992; Louhimo et al. 2001).

In the present study levels of the tumor markers hCGβ and CA125 were elevated in serum and they were both markers of decreased OS, but only elevated serum hCGβ values were associated with worsened DFS. Levels of hCGβ, and stage and histology were all of significant prognostic value as regards OS in multivariate analysis. Serum TATI concentrations were only sparsely elevated and were not of prognostic value for survival.

The serum concentration of CA125 has previously been shown to behave as a prognostic marker for PFTC (Hefler et al. 2000) when using the 75th percentile cut-off value, which in their study was 756 kU/L. On the basis of that study, we also used the 75th percentile cut-off value, which in our study was 1017 kU/L. In our study the CA125 level correlated strongly with stage of the disease and it was therefore not an independent prognostic factor for DFS, although the RR in univariate analysis was similar to that reported by Hefler et al. (2000).

The results of the current study suggest that serum hCGβ concentrations are of prognostic value in PFTC, as has been shown in many other non-trophoblastic cancers (Alfthan et al. 1992; Carter et al. 1994; Carter et al. 1995; Gillott et al. 1996; Vartiainen et al. 2001; Hotakainen et al. 2002; Louhimo et al. 2002; Louhimo et al. 2004a; Louhimo et al. 2004b). Tumors secreting hCGβ are more aggressive and studies on bladder cancer have revealed a higher level of resistance to RT and a higher propensity to metastasize among tumors secreting hCGβ (Iles et al. 1996). The true function of hCGβ is unknown. It cannot stimulate LH/hCG receptor alone, and therefore the effect of hCGβ has to be mediated through some other pathway (Pierce and Parsons 1981). It may act as an autocrine growth factor by inhibiting apoptosis in vitro (Butler et al. 2000), but it does not increase the rate of cell replication. There are suggestions that it could block the transforming growth factor beta (TGFβ) receptor and by that way, apoptosis (Iles 2006). If that is true, this receptor could be a target for anti-tumor vaccines and therapy (Delves et al. 2006).

In conclusion, serum hCGβ and CA125 are useful markers in the diagnosis and follow-up of PFTC and hCGβ is a good marker of prognosis. Among patients with high serum hCGβ levels more aggressive treatments could be used and maybe in the future they could benefit from anti-tumor vaccines and therapy.

The role of infectious factors on the risk of PFTC (III, IV)

The results of the present study involving serological analyses indicate reasons and background other than CTR or HPV infections for PFTC.

The idea of evaluating the significance of CTR and HPV infections in cases of PFTC was based on earlier case reports of tuberculous salpingitis being a possible promoter of PFTC (Gungor et al. 2003) and on studies on the connections between CTR, HPV and other gynecological cancers, mostly cervical cancer (Koskela et al. 2000; Anttila et al. 2001; Paavonen et al. 2003).

The results of some studies have suggested a connection between PID and ovarian cancer (Risch and Howe 1995), but in a study by Parazzini et al. (1996) no association between ovarian carcinoma and PID was found. The only seroepidemiological study (146 cases, 192 controls) concerning CTR infection and ovarian cancer revealed that women with higher levels of CTR antibodies to serovar D had a 90% greater probability of having ovarian cancer (Ness et al. 2003). We did not find an association between an earlier CTR infection and PFTC. These results are in accordance with those reported by Parazzini et al. (1996). We assessed serum CTR antibodies using the MIF method, which has been a tool in epidemiological research on chlamydial infection since 1970 (Wang and Grayston 1970) and is a sensitive and most specific method for laboratory diagnosis of CTR infection, and regarded as the gold standard method for epidemiological research.

Among studies of the risk factors of ovarian cancer, theories concerning ascending factors such as talc (Cramer et al. 1982; Whittemore et al. 1988), asbestos (Graham and Graham 1967), infectious agents or perhaps uterine growth factors (Riman et al. 1998) causing ovarian cancer have been widely proposed, but the mechanism and relevance of these factors still remain poorly understood.

Earlier studies have also revealed an association between HPV and gynecological cancers (Table 9). Human papillomavirus causes cervical cancer (Bosch et al. 1995) and it has also been linked to vulvar (Madeleine et al. 1997) and vaginal (Daling et al. 2002) as well as anal cancers (Daling et al. 2004). The results of studies on the link between ovarian cancer, endometrial cancer and HPV infection are very conflicting. There are studies connecting HPV (mostly HPV16) and endometrial cancer (Lai et al. 1992; Anwar et al. 1996; Zimna et al. 1997; Hisada et al. 2001; Ip et al. 2002) and HPV16 and ovarian cancer (Lai et al. 1992; Anwar et al. 1996; Hisada et al. 2001; Ip et al. 2002; Wu et al. 2003). However, there are many studies that have not revealed an association between HPV and endometrial (Czerwenka et al. 1996; Hording et al. 1997) or ovarian cancer (Leake et al. 1989; McLellan et al. 1990; Beckmann et al. 1991; Anwar et al. 1996; Chen et al. 1999).

Few studies have been conducted concerning serological evidence of the connection between HPV and gynecological cancers others than cervical cancer (Strickler et al. 1998; Hisada et al. 2001) and only a non-significant association has been discovered. No earlier study has involved evaluation of the serological connection between HPV infection and PFTC, but a study of HPV DNA expression in PFTC revealed no HPV DNA in PFTC cases (Heselmeyer et al. 1998).

We measured antibodies to VLPs as markers of exposure to HPV. Serological assays are useful in demonstrating associations in epidemiological studies, although molecular methods are more sensitive. The sensitivity of serological assays using detection of viral DNA as a reference varies between 50% to 75% and the specificity is 95–99% (Dillner et al. 1996; Kjellberg et al. 1999). This may lower the possibility of detecting marginally raised levels of serum HPV antibodies. Levels of antibodies to HPV have been detected to persist in prolonged follow-up (af Geijersstam et al. 1998) and there is no consistent association between HPV seropositivity and age (Wikström et al. 1995; Dillner et al. 1996).

In the present study all serum samples for measurements of CTR and HPV antibodies were taken postoperatively in order to reflect the situation at the time of diagnosis of PFTC. The HPV16 seroprevalence rates were 22% and 21% in cases and controls, respectively, which is relatively high when compared with results in other studies (Cuzick et al. 2000). These aspects ensure that our diagnostic methods for evaluating the effect of an earlier HPV infection on PFTC are adequate, and the results do not suggest that HPV contributes to the

development of PFTC. These are also the primary studies on this subject. However, there might have been some selection bias among control cases that could have influenced our results in studies III and IV, as the control samples were drawn from female employees at HUCH Hospital Area and from female patients seen for a benign colon disease or from patients operated upon because of benign ovarian cysts. In addition, as the PFTC material was relatively small, it may also have had an effect on the results.

Second primary cancers after first PFTC

Second primary cancers are cancers occurring after a prior cancer. They may be attributable to treatment (RT and CT) of the first primary cancer. They may also reflect shared etiologic factors, environmental exposure, host characteristics, and combinations of influences, including common genetic background or gene-environment interactions, and interaction of CT with RT (Travis, 2006a). Chemotherapy sometimes induces leukemia characterized by short latency after a first primary malignancy. Radiotherapy can induce bone marrow malignancies and solid tumors, the most sensitive organs being the breast and thyroid. In contrast to secondary leukemias, the latency period of therapy-associated solid tumors is much longer, usually ≥ 10 years (Travis et al. 1996) and the risk seems to be sustained.

In the present multicenter study we observed increased risks of bladder, breast, colorectal and lung cancer, and non-lymphoid leukemia after PFTC. The clustering of lung and bladder cancer may suggest a shared smoking etiology. The increased risk of these cancers may also be a reflection of earlier RT, and some risk increase could be a reflection of earlier CT with alkylating agents (Travis et al. 2002). The excess of second primary colorectal and breast cancers after PFTC could indicate a shared genetic etiology (Travis et al. 2006b).

These findings are consistent with the results of earlier studies on second cancers after gynecological cancers (Boice et al. 1985; Curtis et al. 1985; Storm and Ewertz 1985; Travis et al. 1996; Travis et al. 1999; Ohno et al. 2006). However, there are no earlier studies on second primary cancers after first PFTC, most likely because of the rarity of the disease. Studies on concomitant presentation of breast cancer, other gynecological cancers and colon cancer among patients with PFTC may suggest a similar hormone responsiveness of those cancers or similar genetic backgrounds (Yoonessi 1979; Alvarado-Cabrero et al. 1999; Baekelandt et al. 2000). In our study the excess risk of breast cancer became apparent more than ten years after PFTC diagnosis and the SIR was not highest in the youngest age groups,

findings that could be explained by an effect of ionizing radiation, and probably unlikely to be explained by genetic susceptibility (Pukkala et al. 2006b).

In conclusion, to the best of our knowledge, the incidence of second primary cancers after first PFTC has not been reported previously. In the present study PFTC patients had a 40% increased risk of developing a new primary cancer, compared with the normal population. In part, the excesses of these second primary cancers may reflect common hormonal responsiveness of these cancers, in part the effects of earlier treatments and in part, lifestyle habits. In the study, common genetic susceptibility for breast cancer and PFTC was not detected, as the SIR for breast cancer was not highest among younger patients and the excess risk of breast cancer occurred relatively late. The late occurrence of second primary cancers reflects the effects of earlier RT. The excesses of breast, colorectal, lung and bladder cancer, as well as non-lymphoid leukemia have to be remembered in follow-up of these cancer patients.

CONCLUSIONS

On the basis of the results these studies the following conclusions can be drawn:

1. The incidence of PFTC increased in Finland during 1953–1997. The increase was highest in the main cities, but the relative rise was highest in rural areas. The incidence was highest in social classes I and II and among academic professions, and lowest among women in rural areas and in women working in farming, forestry and fishing.
2. Parity is a protective factor for PFTC, as is previous sterilization. Previous hysterectomy is not protective as regards PFTC.
3. In multivariate analysis, serum concentrations of hCGβ, and histology and stage were independent prognostic factors for PFTC. An increased serum hCGβ value is a marker of worsened prognosis of PFTC.
4. Past *Chlamydia trachomatis* infection is not related to PFTC.
5. Human papillomavirus infection is not related to PFTC.
6. Second primary cancers among PFTC survivors are bladder, breast, colorectal and lung cancers, and non-lymphoid leukemias, reflecting late effects of radiotherapy and chemotherapy, and maybe a shared smoking etiology. A common genetic or hormonal background may also be possible.

ACKNOWLEDGEMENTS

This study was carried out at the Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Hospital District of Helsinki and Uusimaa, in cooperation with the Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, during the years 2001–2007. My deep gratitude is due to the Director of the Institute of Clinical Medicine, Professor Olavi Ylikorkala, the Administrative Head of Department, Professor Maija Haukkamaa, and to the Director of the Department of Obstetrics and Gynecology, Professor Jorma Paavonen, for providing me with the working facilities.

I address my very warmest gratitude to my supervisor and clinical teacher, Docent Arto Leminen for introducing me to the world of gynecological oncology. His support, patience and guidance, sometimes through a stony path, during all these years have been essential for the work to be finished. I admire his clear and systematic way of working and seeing the essential aspect in scientific studies.

I wish to express my sincere gratitude to Docent Eero Pukkala for introducing me to the world of epidemiology. His guidance and patience during the study years have been essential. I admire his enthusiastic way of working and his huge knowledge of epidemiologic science.

I have had the great privilege of carrying out research in the field of tumor markers under the guidance of Professor Ulf-Håkan Stenman. His excellent expertise, intelligence and warm guidance in the world of tumor markers helped me during these years. I especially enjoyed our discussions in this field.

I want to thank Docent Seija Grénman and Professor Riitta Luoto, the official reviewers, for their positive attitude and constructive review of this manuscript.

I also wish to express my sincere thanks to my co-workers:

Docent Patrik Finne for introducing me to the field of statistics. His enormous help and kind support and friendship during the study years have been essential. Docent Henrik Alfthan, for sharing the first steps in the study, and for sharing his knowledge of hCGβ. Docent Tarja Anttila, for her expertise in the chlamydial analyses and for collaboration. I especially admire her optimistic attitude to life. Docent Pentti Koskela, for providing me with the

possibility to learn the HPV assays and Professor Matti Lehtinen, for collaboration in the HPV world and for interesting discussions around this field. Jyrki Jalkanen, Ph.D., and Tiina Sorvari, M.D., for their valuable collaboration. Reijo Sund, M.Sc., for his expert statistical knowledge in the epidemiologic study, and Docent Mika Gissler for his knowledge of register research. All my collaborators abroad in the multicenter study: Ghislaine Scélo, Lene Mellemkjaer, Kari Hemminki, Elisabete Weiderpass Vainio, Mary McBride, Vera Pompe-Kirn, Elisabeth Tracey, David Brewster, Erich Kliewer, Jon Tonita, Chia Kee-Seng, Jon Jonasson, Carmen Martos, Paolo Boffetta and Paul Brennan, whose help made this work possible. Terhi Ahola, M.D.,Ph.D., and Mervi Väisänen-Tommiska, M.D.,Ph.D, for their enormous help and support in the makeup and proofreading of this thesis. Nicholas Bolton, Ph.D., for his quick and skillful revision of the language.

This study was financially supported by grants from the Research Funds of Helsinki University Central Hospital, the Finnish Medical Foundation, the Finnish Foundation of Gynecology and Obstetrics, the Finnish Cultural Foundation, the Finnish Cancer Foundation, the Research Foundation of Orion Corporation, the Schering Research Foundation, the Lilly Foundation, the National Cancer Institute and the Association of Gynecological Surgery.

I also want to thank:
Taina Grönholm and Anne Ahmanheimo for helping me collect the serum samples, for teaching me and for performing the hCGβ assays as well as assays of other tumor markers. Laila Selkinen, Nina Hedkrok and Raili Alanne for their kind assistance in every possible way. All the nurses and midwives who helped me find control subjects. The nurses at the oncology ward, for all their support and for a warm working atmosphere. All friends and colleagues at Helsinki University Central Hospital, for encouragement and support during the years. All friends outside work, for their encouragement and help in so many ways.

My late parents, who created the grounds where the strength of working is based. My sisters Kristina and Susanna and their families; this is what stays.
Finally, my children Teo, Taru and Krista, the most important people in my life. Your presence reminds me every day what is important in life.

Espoo, March 2007

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Int. J. Cancer: **104,** 643–645 (2003)

Publication of the International Union Against Cancer

SOCIODEMOGRAPHIC DETERMINANTS OF INCIDENCE OF PRIMARY FALLOPIAN TUBE CARCINOMA, FINLAND 1953–97

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Primary fallopian tube carcinoma is very rare. In Western countries, it accounts for about 1% of all female genital malignant tumors. Its etiology remains poorly known, but high parity is considered to be protective. We studied determinants of incidence of primary fallopian tube carcinoma in Finland. Incidence rates for primary fallopian tube carcinoma, according to the population based Finnish Cancer Registry, from 1953– 97 were assessed by age, year of diagnosis, and type of residential area. Standardized incidence ratios (SIRs) for the years 1971– 95 were calculated by occupation and social class variables taken from the 1970 Population Census. There were 485 cases of primary fallopian tube carcinoma registered during 45 years. The age-adjusted incidence rate increased from 1.2/1,000,000 in 1953–57 to 5.4/1,000,000 in 1993–97. This 4.5-fold increase in incidence rate corresponds to a 7-fold increase in the number of new cases. The increase is attributable to the age group beyond 55 years, the peak incidence occurring between 60–64 years. Although the relative increase in incidence rate has been larger in rural areas than in cities, the rate in the latter remains 2-fold. Women in the 2 highest social classes had a 1.8-fold incidence (95% CI = 1.2–2.6) as compared to the lowest social class. Women in agriculture and those not working outside the home had only half the cancer incidence of those in academic or clerical occupations. The incidence of primary fallopian tube carcinoma increases in Finland. Evidently, the incidence has increased simultaneously with the affluence of urban life. Part of the variation in incidence correlates with variation in parity.

Key words: *primary fallopian tube carcinoma; incidence; social class; occupation*

Primary fallopian tube carcinoma (PFTC) is a very rare but highly aggressive disease, reported to comprise 0.1–1.1% of all female genital malignancies.[1] PFTC was described for the first time by Renaud in 1847.[2] Although its etiologic factors are largely unknown, they have been considered to be similar to those of ovarian carcinoma. Histologically, most PFTCs are pure adenocarcinomas, the main type being serous adenocarcinoma. Occasional cases of endometrioid, clear cell, transitional cell, and glassy cell carcinomas have been reported.[3]

Finland is an industrialized country with 5.2 million inhabitants. Most Finns live in urban communities. Finland is characterized by a relatively homogenous population and an effective nearly free-of-charge healthcare system. The nationwide population-based cancer registry allowed us to study incidence characteristics of PFTC over a period of 45 years in Finland.

MATERIAL AND METHODS

More than 99% of all cancer cases have been reported to the Finnish Cancer Registry 1953.[4] In the 1990s, about 95% of the cases were microscopically confirmed, and about 1% of the cases based on death certificate only.[5] The Registry obtains information from hospitals and other institutions with inpatient beds, general practitioners, and pathology and cytology laboratories. The Finnish Cancer Registry also receives copies of all death certificates in which cancer is mentioned. Notification of new cancer cases to the Cancer Registry is mandatory by law. From this register, we collected all patients reported to have PFTC in 1953–1997. The incidence rates, age-standardized to the world population,[6] were calculated by calendar period and urbanization level of the place of residence.

The methods for calculating the standardized incidence ratios (SIRs) in relation to occupation and social class have been described in detail by Pukkala .[7] Briefly, Statistics Finland organized an official census of the Finnish population in 1970.[8] The questionnaire included information on occupation, which was coded into more than 400 occupational categories. Four social classes were defined on the basis of education, occupation, industrial status, and industry groupings.[8,9] Financially dependent persons (*e.g.*, housewives and students) were classified by the occupation of their supporter.

The four social classes were defined as follows:

1. Managers and other higher administrative or clerical employees, farmers owning more than 50 hectares of land;
2. Lower administrative or clerical employees, small-scale entrepreneurs, farmers owning 15–49.9 hectares of land;
3. Skilled and specialized workers, farmers owning 5–14.9 hectares of land;
4. Laborers, farm and forestry workers, institution inmates, farmers owning <5 hectares of land, retired persons, whose former occupation was unknown.

The cancer records of the Finnish Cancer Registry from 1971–95 for persons born in 1906–45 were linked with the census data. The expected numbers of cases were calculated by multiplying the stratum-specific number of person-years by the respective calendar period and birth cohort-specific incidence rate of all Finnish women. The SIR values were the ratio of the observed to the expected number of cases. Confidence intervals (CI) were defined with the assumption that the observed number of cases followed Poisson distribution.

RESULTS

From 1953–97, 485 patients with PFTC were identified. Fifteen cases of the PFTC were found during the 5-year period 1953–57 and 108 during 1993–97, indicating a 7-fold increase in the number of new cases. The age-adjusted incidence increased in the 1980s and 1990s (Table I). In rural areas, the incidence was lower, but the relative rise was higher than in cities (Fig. 1). The main increase was in the oldest age groups (Fig. 2). During 1953–67 the peak incidence occurred in groups aged 50–54 years, whereas

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Received 24 May 2002; Revised 4 October 2002; Accepted 10 October 2002

DOI 10.1002/ijc.10970

TABLE I – ANNUAL NUMBER OF NEW CASES AND FEMALE POPULATION AT RISK, AND INCIDENCE RATES PER 1,000,000 FOR PRIMARY FALLOPIAN TUBE CARCINOMA IN FINLAND BY PERIOD OF DIAGNOSIS

Period	*n*	Population	Rate[1]
1953–57	15	11,011,700	1.2
1958–62	31	11,508,000	2.3
1963–67	47	11,888,100	3.3
1968–72	40	11,933,500	2.5
1973–77	39	12,174,800	2.4
1978–82	46	12,378,000	2.7
1983–87	69	12,655,100	3.6
1988–92	90	12,869,900	4.3
1993–97	108	13,119,000	5.4

[1]Adjusted for age to the world standard population.

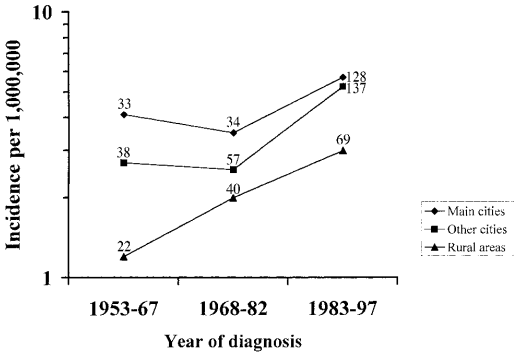

FIGURE 1 – Incidence rates per/1,000,000 of primary fallopian tube cancer in different areas in Finland expressed in 15-year periods from 1953–97, adjusted for age to the world standard population. Main cities: Helsinki, Tampere, Turku. Number of cases in each category are expressed in the figure.

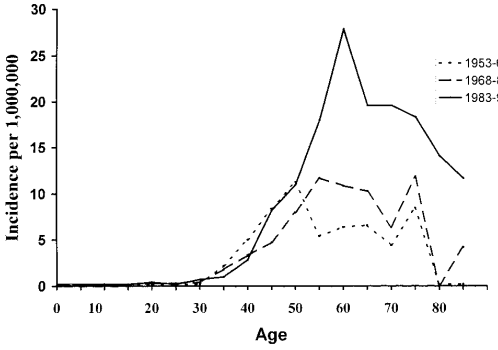

FIGURE 2 – Age-specific incidence rates per/1,000,000 of primary fallopian tube cancer in Finland expressed in 15-year periods from 1953–97.

during 1983–97 the incidence was highest between 60–64 years of age.

There were 268 PFTC cases (all being a part of the total sample) diagnosed in 1971–95 in women born 1906–45, for which information on social class and occupation were available from Population Census 1970. The SIRs markedly increased toward higher social classes: the ratio of the combined SIR of Classes I and II compared to that of Class IV was 1.8 (95% CI = 1.2–2.6) (Table II). Occupational branches "health care, technical, physical science, social science, humanistic, and artistic occupations" and "administrative and clerical work" were associated with high SIRs for PFTC, while "farming, forestry and fishing" was associated with a low risk, as were economically inactive women (Table III). From specific occupations, significantly high SIRs were observed for private secretaries (SIR 4.4, 95% CI = 1.4–10), nurses (4.0, 95% CI = 2.1–7.0), hairdressers and barbers (3.9, 95% CI = 1.3–9.2), and book-keepers and accountants (3.6, 95% CI = 1.6–7.1).

TABLE II – NUMBER OF PRIMARY FALLOPIAN TUBE CARCINOMA CASES OBSERVED DURING 1971–1995 AMONG WOMEN BORN BETWEEN 1906 AND 1945 BY SOCIAL CLASS[1]

Social class	Observed	SIR (95% CI)[2]
I	25	1.27 (0.81–1.87)
II	95	1.28 (1.04–1.57)
III	114	0.89 (0.74–1.06)
IV	34	0.73 (0.51–1.02)

[1]All women in Finland = 1.0.–[2]Standardized incidence ratio.

TABLE III – PRIMARY FALLOPIAN TUBE CARCINOMA CASES OBSERVED DURING 1971–1995 AMONG WOMEN BORN BETWEEN 1906 AND 1945 BY THE MAIN OCCUPATIONAL CATEGORIES[1]

Occupation	Observed *n*	SIR (95% CI)[2]
Academic[3]	37	1.63 (1.15–2.25)
Administrative and clerical	35	1.60 (1.12–2.23)
All economically active persons	180	1.11 (0.96–1.28)
Transport and communications	6	1.09 (0.40–2.37)
Whole population	268	1.00 (0.88–1.12)
Services	32	1.00 (0.69–1.42)
Sales professions	16	0.98 (0.56–1.59)
Industrial and construction work	27	0.95 (0.63–1.38)
Economically inactive[4]	88	0.83 (0.66–1.02)
Farming, forestry, and fishing	27	0.79 (0.52–1.14)

[1]All women in Finland = 1.0.–[2]Standardized incidence ratio.–[3]Health care, technical, physical science, social science, humanistic, and artistic occupations.–[4]Largely housewives.

DISCUSSION

Our results show a 2-fold increase in the incidence of PFTC during the last 15 years. At the end of the study period, the incidence was 5.4/1,000,000. In the United States during the period 1995–99 the SEER program reported an age-adjusted incidence rate of 3.3/1,000,000 among Caucasian women.[10] In Denmark, the incidence rate around 1980 of 2.9/1,000,000[11] was quite close to the respective Finnish rate. The age patterns in Denmark and in Finland resemble each other, with the peak incidence occurring between the ages of 60–64 years, whereas in the US, the peak incidence was highest between the ages of 70–74 years.[10]

In our study, the incidence rate was greatest in urban areas and in higher social classes. Professions with a high level of education or with compulsory health control, such as medical care personnel, had an increased risk of PFTC, which could be a consequence of a higher identification rate due to greater alertness and routine visits to gynecologists.

Because no dramatic changes in the diagnostic procedures of PFTC have occurred in recent decades, improved procedures cannot explain the rising incidence of this cancer. From the 1950s–1980s, however, carcinomas were more often detected to be inoperable during laparotomy. As only biopsies were taken from those inoperable cases, it was often impossible for the pathologist to differentiate between ovarian and tubal carcinoma, leading to misclassification of the tubal tumor as ovarian carcinoma. Ovarian and tubal carcinomas share many features. In organogenesis, they both develop from the Müllerian duct and are histologically nearly identical. Clinically, they have a tendency toward invasive behav-

ior, early dissemination throughout the peritoneal cavity, and poor overall prognosis. PFTC tends to be even more aggressive than ovarian cancer, and in less than 4% of cases is the diagnosis made before primary surgery.[11,12]

PFTC and ovarian cancer have a similar etiology. Exposure to high levels of gonadotropins, incessant ovulation, and infertility increase the risk of ovarian cancer, whereas high parity, breast feeding, the use of oral contraceptives, tubal ligation, and hysterectomy seems to provide protection.[13–20] Recent studies have also found evidence that BRCA1 and BRCA2 germline mutations increase the risk of PFTC as well as of ovarian carcinoma.[21–24] The pelvic inflammatory disease (PID) appears to be a risk factor for development of ovarian carcinoma,[25,26], and an association between PID and PFTC has also been suggested.[27]The observed incidence pattern of PFTC matches the pattern of parity in Finland; the average number of children has decreased and is highest among economically inactive women and women in agriculture.[7]So far, however, no case-control studies have been published concerning PFTC and PID and parity.

In conclusion, the incidence of PFTC in Finland has risen markedly during the last decades and is clearly associated with higher socioeconomic status. Etiological factors explain part of the increase, but other explanations must be explored to elucidate the variation in its entirety.

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II

Research Article

Tumor Biology

Tumor Biol 2006;27:43–49
DOI: 10.1159/000090155

Received: April 15, 2005
Accepted: August 11, 2005
Published online: December 8, 2005

Preoperative Serum hCGβ as a Prognostic Marker in Primary Fallopian Tube Carcinoma

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Key Words
Primary fallopian tube carcinoma · Tumour-associated trypsin inhibitor · Human chorionic gonadotropin

Abstract
Objectives: It was the aim of this study to evaluate the prognostic value of the pretreatment serum concentrations of the β-subunit of human chorionic gonadotropin (hCGβ), CA 125 and tumour-associated trypsin inhibitor (TATI) in primary fallopian tube carcinoma (PFTC). ***Methods:*** The pretreatment serum concentrations of hCGβ, CA 125 and TATI were analyzed in serum samples from 60 women with a mean age of 61 years, treated for PFTC between 1985 and 2000. Of the 91 patients treated during this period, 31 were excluded because no serum sample was available. The patients were followed-up for recurrence and survival until February 14, 2003. The prognostic value of the serum markers were compared with those of stage, grade and histological type. ***Results:*** The median survival time was 27 months and the overall 5-year survival rate 33%. Stage and size of the residual tumour (<1 vs. ≥1 cm) predicted both overall and disease-free survival ($p < 0.050$). Histology (serous vs. others) ($p = 0.023$) also influenced overall survival. Overall 5-year survival was 38% when serum hCGβ was below 3.5 pmol/l, while it was 18% when the level was higher ($p = 0.052$). The corresponding disease-free 5-year survival was 38 and 20%, respectively ($p = 0.014$). Patients with CA 125 values above 1,017 kU/l had an overall 5-year survival of 39% as compared with 14% for those with lower values ($p = 0.009$), while the disease-free survival was 37 and 23%, respectively ($p = 0.096$). Serum TATI was not a prognostic marker. Serum concentrations of hCGβ and CA 125 correlated significantly with stage ($p = 0.049$ and $p = 0.050$, respectively). In multivariate Cox proportional hazards regression analysis, only hCGβ, stage and histology emerged as independent prognostic factors. ***Conclusions:*** Clearly elevated serum concentrations of hCGβ and CA 125 predict survival in fallopian tube carcinoma, but in multivariate analyses, only hCGβ is a prognostic factor independent of stage and histology.

Introduction

Primary fallopian tube carcinoma (PFTC) is a rare gynaecological carcinoma constituting 0.1–1.1% of all neoplasms of the female genital tract [1], but its incidence is increasing. In Finland, it has increased from 1.2/1,000,000 in 1953 to 5.4/1,000,000 in 1997 [2]. Only 4% are correctly diagnosed preoperatively and most of

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Table 1. Clinical characteristics of 60 patients with PFTC

Parameter	n	%
Stage		
I	7	10
II	8	13
III	34	58
IV	11	18
Grade		
1	5	8
2	19	32
3	35	58
No data	1	2
Histological type		
Serous	48	80
Mucinous	0	0
Endometroid	1	2
Clear cell	0	0
Anaplastic	9	15
Mixed	2	3
Tumour size, cm		
<2	4	6
2–5	9	15
5–10	19	32
>10	28	46
Residual tumor size, cm		
None	21	35
<0.5	1	2
0.5–1	1	2
1–2	3	5
>2	25	42
Peritoneal carcinosis	8	13
No data	1	2

the cases are detected at an advanced stage. Despite advances in therapy, the prognosis is poor, the overall 5-year survival rate being 33–57% [3–6]. The size of the residual tumour, clinical stage, histological grade and age of the patient have been shown to affect prognosis [3, 7–9].

Serum tumour markers are very valuable for monitoring the clinical course of gynaecological cancers and CA 125 plays an important role in diagnosis and follow-up of PFTC as well as in ovarian carcinoma [6, 10]. Changes in CA 125 levels during the course of disease reflect the response to therapy, and in a recent study, a CA 125 level above 756 U/ml (75th percentile) was found to be an independent prognostic factor for disease-free survival (DFS) and overall survival in PFTC [8]. There are no reports of the prognostic value of other tumour markers in PFTC.

Human chorionic gonadotropin (hCG) is a glycoprotein consisting of two subunits, i.e. the α- and β-subunit. hCG is a very useful marker for monitoring pregnancy, pregnancy-related disorders and trophoblastic disease, but it is very rarely useful in non-trophoblastic malignancies [11]. In these, the free β-subunit of hCG (hCGβ) in serum is fairly often elevated, e.g. in ovarian carcinoma, elevated serum hCGβ levels have been observed in 30–40% of the patients [12–14]. Furthermore, hCGβ is an independent prognostic factor in ovarian, colorectal and renal cell carcinoma [14–16]. Elevated serum levels of hCGβ correlate with excretion of the core fragment of hCGβ, a degradation product of hCGβ into urine [17], and elevated urinary levels of the core fragment of hCGβ reflect the prognosis in vulvar and cervical carcinoma [18, 19].

Tumour-associated trypsin inhibitor (TATI) is a marker that is elevated in various cancers. Expression of TATI is associated with expression of tumour-associated trypsin. Trypsin expression is generally associated with an aggressive disease. TATI reflects trypsin expression and serum TATI has been shown to be an independent prognostic marker for ovarian [14, 20], renal [16] and bladder cancer [21].

The purpose of the present study was to clarify the prognostic value of preoperative hCGβ in patients with PFTC using a highly sensitive and specific immunofluorometric assay. As reference markers we used CA 125 and TATI.

Patients and Methods

Patients

Ninety-one consecutive patients treated for PFTC in our hospital between 1985 and 2000 were studied. Patient data were retrieved by detailed chart review. The clinical characteristics of the patients are shown in table 1. The patients did not receive chemotherapy prior to surgery. Thirty-one of 91 patients (34%) were excluded from the study because a preoperative serum sample was not available. In order to exclude selection bias, we studied the overall survival of patients with and without preoperative hCGβ values and there was no statistically significant difference ($p = 0.929$), median survival being 29 and 36 months, respectively. The distribution of stage ($p = 0.294$), grade ($p = 0.789$), tumour size ($p = 0.105$), size of the residual tumour ($p = 0.929$) and histological type (serous adenocarcinomas vs. others; $p = 0.165$) did not differ between the groups.

The patients were followed up for recurrence and survival until February 14, 2003. Preoperative serum measurements of hCGβ, CA 125 and TATI were available in 60, 57 and 59 cases, respectively. Samples were drawn 1–75 days (median 15 days) before surgery. Mean age of the patients was 61 years (range 40–83). Stag-

Table 2. Number of samples with elevated serum concentrations of hCGβ, CA 125 and TATI according to stage

	hCGβ				CA 125				TATI			
	>3.5 pmol/l (75 percentile)		>2 pmol/l		>1,017 kU/l (75 percentile)		>35 kU/l		>1.6 nmol/l (75 percentile)		>2 nmol/l	
	n	%	n	%	n	%	n	%	n	%	n	%
Stage												
I	0/7	0	1/7	14	0/7	0	4/7	57	0/7	0	0/7	0
II	1/8	12	2/8	25	1/8	12	6/8	75	2/8	25	1/8	12
III	10/34	29	14/34	41	9/31	29	28/31	90	9/33	27	7/33	21
IV	4/11	36	5/11	45	4/11	36	11/11	100	4/11	36	4/11	36
Total	15/60	25	22/60	37	14/57	25	49/57	86	15/59	25	12/59	20

Figures denote elevated number/total number of samples.

ing was performed according to the FIGO criteria with pelvic and para-aortic lymphadenectomy whenever possible. Stage, grade, histological findings, tumour size and size of the residual tumour were recorded (table 1). In 8 cases, surgery was limited to explorative laparotomy (histological sampling) either because of an unresectable condition or peritoneal carcinosis. In 1 case, the size of the residual tumour was not recorded. All patients except 2 received platinum-based combination chemotherapy as adjuvant therapy: 1 patient denied chemotherapy and another died before chemotherapy could be started. Nine patients had other previous cancers: 5 of them breast cancers, 2 gastrointestinal cancers and 2 other cancers of unknown origin. All of them were cured before the diagnosis of PFTC. No patients with a previous cancer were known to have any genetic background. Sixty-seven patients out of 91 died. Of those 67 patients who died during the follow-up, 62 died of their cancer, 1 of chemotherapy, 3 of other diseases and in 2 the cause was unknown.

Methods

hCGβ in serum was quantified with an in-house time-resolved immunofluorometric assay [22] with a detection limit of 0.5 pmol/l. Cross-reaction of hCG in the assay for hCGβ is <0.1%. Inter-assay coefficient of variation is <12% in the hCGβ, range 2–3,000 pmol/l. The upper reference limit based on the 97.5th percentile for apparently healthy women was 2.0 pmol/l. The serum concentrations of hCGβ are not age dependent [23]. The median pretreatment serum hCGβ level was 1.25 pmol/l. For the purpose of evaluating the prognostic value of hCGβ before surgery, the 75th percentile of the pretreatment level (3.5 pmol/l) was selected as the cut-off level [8].

CA 125 was measured by an immunoradiometric assay (Centocor, Malvern, Pa., USA) until October 1995. After that, quantitation was performed on an automatic analyzer (Immuno1®, Bayer, Tarrytown, N.Y., USA). Correlation between the two assays was good (r = 0.91). A cut-off value of 35 kU/l was used for both assays. The median pretreatment value was 355 kU/l and the 75th percentile pretreatment level used for prognostic analysis was 1,017 kU/l.

TATI was measured by radioimmunoassay (Orion Diagnostica, Espoo, Finland), and a cut-off value of 2 nmol/l (13 μg/l) was used. The median pretreatment level was 1.6 nmol/l.

Statistical Methods

The χ^2 test was used to compare distributions of categorical variables between patients with serum marker measurements and those without. For comparing frequencies of elevated serum marker levels between stages, the χ^2 test for trend was used. Follow-up of the patients with preoperative serum samples started at the time of diagnosis and ended at the time of death (n = 43) or at the latest on February 14, 2003 (n = 17), when survival was checked with the Population Register Centre in Finland. The median follow-up time for all patients was 30 months (range 0.3–173) and for those alive it was 60 months (range 37–168). In analysis of overall survival, death due to any cause was defined as an event. When analyzing DFS, the event was relapse of the disease.

Probability of survival was estimated according to the Kaplan-Meier method. Differences in survival probabilities between groups were assessed using the log-rank test. Multivariate modelling of survival probability was performed using Cox proportional hazards regression analysis [24]. Cox regression was also used univariately for calculation of the relative risks of dying. Serum marker concentrations were analyzed and transformed to binary variables by testing values between the 70th and 80th percentiles. These cut-offs gave similar results, and results for the 75th percentile are shown. Two-sided p values <0.05 were considered statistically significant.

Results

Serum Marker Concentrations

The serum concentrations of hCGβ were elevated in 37% of all cases as compared to 90% of CA 125 and 20% of the TATI values. For prognostic analysis, we used the 75th percentile for all markers [8]. The frequencies of

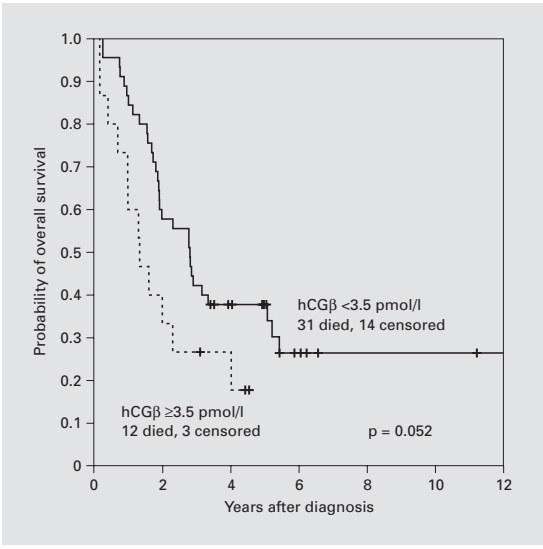

Fig. 1. Effect of preoperative serum hCGβ concentration on overall survival of PFTC patients.

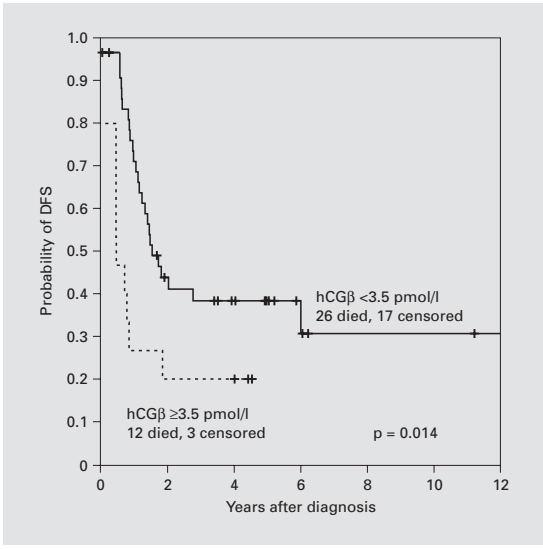

Fig. 2. Effect of preoperative serum hCGβ concentration on DFS in PFTC patients.

marker values exceeding the 75th percentile in various disease stages were similar for the three markers studied (table 2).

Survival Analyses

The overall 5-year survival rate was 33% and it was related to stage (p = 0.050). The disease-free 5-year survival was also 33%, which reflects the aggressiveness of the disease. The size of the residual tumour was an important prognostic factor; the overall 5-year survival for patients with a residual tumour <1 or ≥1 cm was 51 and 20%, respectively (p = 0.003). In patients with a serous carcinoma, the overall 5-year survival rate was 37% compared with 17% in those with other tumour types (p = 0.023). In Kaplan-Meier analysis, the most important prognostic factors for disease-free 5-year survival were the size of the residual tumour (p = 0.013) and stage (p = 0.014).

The overall 5-year survival was 38% when hCGβ was below the 75th percentile and 18% when it was higher (p = 0.052) (fig. 1), while the disease-free 5-year survival was 38 and 20%, respectively (p = 0.014) (fig. 2). Patients with serum CA 125 values above the 75th percentile also had significantly shorter overall 5-year survival, i.e. 14 vs. 39% (p = 0.009) (fig. 3), and a disease-free 5-year survival of 23 and 37%, respectively (p = 0.096). Clearly elevated serum concentrations of TATI were rare and this marker did not have prognostic value.

Cox Regression Analysis of Prognostic Factors

In a univariate Cox regression model, the size of the residual tumour (p = 0.004), serum CA 125 (p = 0.012) and stage (stage IV, p = 0.018) were significantly associated with overall survival, while serum hCGβ (p = 0.019), stage III–IV (p = 0.020), stage IV (p = 0.025) and size of the residual tumour (p = 0.019) were all associated with DFS (table 3). When all the variables were fitted as multiple variables in the same model, only hCGβ and the histology of the tumour were independent prognostic factors for overall survival and only hCGβ for DFS (table 4). Stage and size of the residual tumour were strongly correlated (p <0.001) disturbing each other in the multivariate analysis, and therefore, the latter was excluded from the Cox model. In a backward stepwise Cox multivariate analysis, hCGβ, stage and histology emerged as independent prognostic factors (table 5).

Table 3. Univariate Cox regression model of prognostic factors in PFTC

Factor	Overall survival			Relapse-free survival		
	risk ratio	95% CI	p value	risk ratio	95% CI	p value
Size of residual tumour	2.72	1.38–5.37	0.004	2.37	1.16–4.85	0.019
CA 125 >1,017 kU/l	2.44	1.22–4.90	0.012	1.83	0.87–3.86	0.109
Stage IV versus other stages	2.29	1.15–4.58	0.018	2.32	1.11–4.85	0.025
Stage III–IV	2.03	0.93–4.41	0.073	3.08	1.19–7.96	0.020
hCGβ >3.5 pmol/l	1.94	0.98–3.82	0.057	2.30	1.14–4.62	0.019
Age >65 years	1.29	0.68–2.45	0.432	1.00	0.49–2.02	0.998
Grade 3	0.84	0.45–1.56	0.589	0.74	0.38–1.43	0.374

Table 4. Multivariate Cox regression model of prognostic factors for overall survival and DFS in PFTC

Factor	Overall survival			DFS		
	risk ratio	95% CI	p value	risk ratio	95% CI	p value
Histology	3.17	1.27–7.95	0.013	1.60	0.59–4.31	0.349
hCGβ >3.5 pmol/l	2.80	1.03–7.63	0.043	3.07	1.04–9.03	0.041
Stage IV	2.17	0.95–4.95	0.065	1.90	0.79–4.54	0.149
CA 125 >1,017 kU/l	1.91	0.83–4.39	0.127	1.52	0.62–3.69	0.352
Size of residual tumour	1.86	0.79–4.36	0.152	1.49	0.60–3.66	0.387
Age >65 years	1.65	0.77–3.50	0.193	1.06	0.47–2.35	0.886
TATI >1.6 nmol/l	0.57	0.21–1.52	0.260	0.69	0.25–1.86	0.462
Grade 3	0.48	0.22–1.03	0.060	0.54	0.24–1.21	0.136

Table 5. Significance of prognostic factors when fitted in Cox backward stepwise regression model as multiple variables

Factor	Overall survival		p value
	risk ratio	95% CI	
Histology	2.71	1.26–5.83	0.010
Stage IV	2.47	1.21–5.02	0.012
hCGβ >3.5 pmol/l	2.49	1.22–5.09	0.012

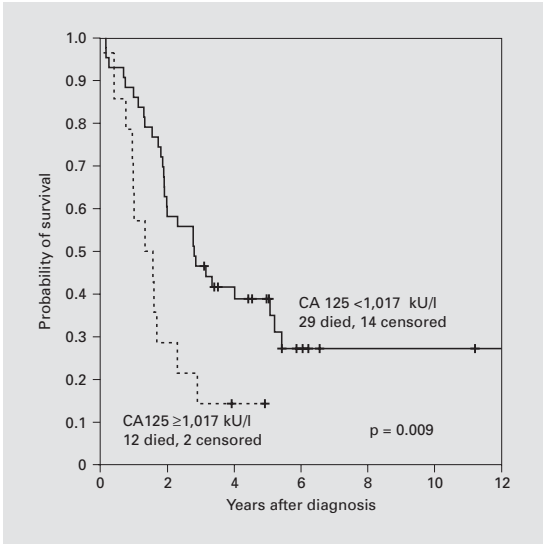

Fig. 3. Effect of preoperative serum CA125 concentrations on overall survival in PFTC patients.

Discussion

An elevated serum concentration of hCGβ has been shown to be an independent prognostic factor in many carcinomas [15, 16, 25, 26] and especially in ovarian carcinoma [14]. Therefore, we studied whether it also predicts prognosis in PFTC, which in many respects resembles ovarian carcinoma. There are only a few reports on prognostic markers in PFTC [8, 26] and our study is the first to investigate the prognostic role of hCGβ in this disease. As the cut-off for analysis of prognosis, we used the 75th percentile, which has been used in an earlier study on CA 125 [8], but results with cut-offs of the 80th and 70th percentiles were similar. Our results show that serum hCGβ, stage and histology are the strongest independent prognostic factors in PFTC.

CA 125 was also a significant prognostic factor for overall survival, which is in accordance with results from an earlier study by Hefler et al. [8]. However, in our study, CA 125 correlated strongly with stage and was therefore not an independent prognostic factor for DFS although the risk ratio in univariable analysis was similar to that in the study of Hefler et al. [8]. In our study, as in Hefler's study, the number of patients is quite small, and this may explain the differences in DFS between these two studies. Interestingly, serum TATI was not a prognostic factor for PFTC, although it has been shown to be an independent prognostic factor for ovarian carcinoma [20], especially in stage III disease [28]. In ovarian cancer, TATI expression is associated with expression of tumour-associated trypsin [29], which is not known to occur in PFTC. This may reflect a difference in the biology of these tumours.

The mean age of 61 years of the patients in the present series is similar, while the stage distribution was somewhat different from that reported in other studies [1, 3, 9]; only 10% of our patients had stage I disease as compared to 20–42% in earlier studies [3, 4, 26]. Well-differentiated tumours were observed in 8%, while 32% had grade 2 and 58% grade 3 tumours, which is in concordance with earlier studies [4]. The distribution of histological subgroups is also comparable with that in earlier studies [29, 30], with 80% serous adenocarcinomas. The presence of another carcinoma before PFTC has also been reported in other studies: 11% in the study of Eddy et al. [30], and 17 of 115 (15%) in the study of Alvarado-Cabrero et al. [31], 6 of which (5%) being breast cancers. In our study, there were 9 cases (15%) of a second malignancy, 5 of them breast cancers. So far, these are the only studies reporting on the simultaneous occurrence of these carcinomas. The responsiveness of both tubal and breast epithelium to ovarian hormones may provide a theoretical background for this association [30]. Interestingly, like breast cancer, PFTC has been linked to mutations in the BRCA-1 gene [32].

The strong correlation between serum hCGβ and prognosis is intriguing. Some mechanisms through which hCGβ could affect tumour aggressiveness have recently been elucidated. hCGβ may exert antiapoptotic activity [33], and suppression of hCGβ expression reduces tumour growth of hCGβ-expressing tumours [34]. Furthermore, immunization with hCGβ vaccines has provided promising results in patients with colon carcinoma [35]. It is tempting to speculate that these mechanisms could explain why elevated serum levels of hCGβ are associated with adverse prognosis in PFTC as well as in many other malignancies.

Elevated levels of serum hCGβ have been observed in many nontrophoblastic tumours and most often in pancreatic (72%) and biliary carcinomas (86%) [17], which both are rapidly progressive cancers with very poor prognosis. In ovarian carcinoma, the 5-year survival was found to be 80% if serum hCGβ was normal and only 22% when hCGβ was elevated and, in those with stage III and IV and minimal residual disease, 5-year survival was 75% if the hCGβ level was normal and 0% if it was elevated [14]. Also in PFTC, hCGβ is a strong prognostic factor and contrary to stage and grade, it can be determined before surgery. However, so far, a limitation in the use of hCGβ is the paucity of sufficiently sensitive commercially available assays.

The number of patients in our study is limited, because PFTC is so rare. In comparison with other studies concerning PFTC, it is one of the largest. Because of the aggressiveness of this disease, we found it very important to evaluate the prognostic value of the tumour markers hCGβ and CA 125.

In conclusion, both hCGβ and CA 125 predict survival in PFTC, but in our study, only hCGβ provided prognostic value additional to that based on stage and histology. Thus, serum hCGβ is a potential marker for the selection of patients with PFTC for experimental treatment modalities. If hCG immunotherapy proves to be useful, it will be important to study whether tumour responsiveness to this therapy can be evaluated on the basis of the serum concentrations of hCGβ.

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EUROPEAN JOURNAL OF CANCER 42 (2006) 1835–1838

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Past chlamydial infection is not associated with primary fallopian tube carcinoma

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ARTICLE INFO

Article history:
Received 24 November 2005
Accepted 29 November 2005
Available online 12 June 2006

Keywords:
Primary fallopian tube carcinoma
Chlamydia trachomatis
Chlamydia pneumoniae

ABSTRACT

We conducted a retrospective seroepidemiological study to evaluate the relationship between past chlamydial infection and primary fallopian tube carcinoma (PFTC). Postoperative serum samples were drawn from 79 consecutive patients treated for PFTC in 1985–2000. For each case two controls were selected. Serum samples were analysed for IgG antibodies to different *C. trachomatis* serotype pools and to *C. pneumoniae*. Seropositivity in general or serum antibody levels to different *C. trachomatis* serovars or *C. pneumoniae* did not differ between PFTC patients and controls. The lack of association between anti-chlamydial antibodies and PFTC suggests that past chlamydial infection does not play a role in the etiopathogenesis of PFTC. However, because chlamydial infection is common at young age and PFTC develops decades later, we cannot definitively exclude the possibility that *C.trachomatis* contributes to the development of PFTC.

1. Introduction

Primary fallopian tube carcinoma (PFTC) is a rare but aggressive disease, comprising 0.1–1.1% of female genital malignancies.[1] The age-adjusted annual incidence in Finland has increased from 1.2 per 1,000,000 women in 1953 to 5.4 per 1,000,000 women in 1997.[2] The incidence has increased especially among women in higher social classes and among those living in urban areas.[2] The aetiological factors are largely unknown, but may be similar to those of ovarian cancer.

Chlamydia trachomatis infection is the most common sexually transmitted bacterial infection (STI),[3] causing salpingitis and pelvic inflammatory disease (PID).[4,5] *Chlamydiae* are common intracellular bacteria and can cause chronic or persistent infections.[6] Chronic infections may predispose to malignant growth.[7] *C. trachomatis* has already been linked to cervical carcinoma.[8,9] History of PID has been linked to ovarian carcinoma.[10–12] Thus, an association between *C. trachomatis* and PFTC is biologically plausible. The purpose of this study was to evaluate the role of *C. trachomatis* in PFTC.

2. Patients and methods

The study population consisted of 79 consecutive patients treated for PFTC at the Department of Obstetrics and Gynaecology, University Hospital, Helsinki, between 1985 and 2000. Data were collected by systematic chart review. The patients had not received chemotherapy prior to surgery. Staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) criteria. Pelvic and

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doi:10.1016/j.ejca.2005.11.041

para-aortic lymphadenectomy was performed whenever possible. Stage, grade, histological findings, tumour size, and size of the residual tumour were recorded. Serum samples were drawn at a median of 36 d (interquartile range 28–55 d) after primary surgery. For each case, two controls were selected randomly from women matched for age at serum sampling (±5 years), and who had no cancer diagnosis. For the five youngest patients the age criterion had to be somewhat relaxed due to lack of suitable controls. Because two blood samples were drawn from the same control subject by mistake, two cases had only one control. Thus, the total number of controls was 156. Ninety-one serum samples were from control patients from the Helsinki City Maternity Hospital, operated for a benign gynaecological disease. Sixty-one control archival serum samples were from patients coming to an examination for a benign colon disease (30 controls) or were female employees at Helsinki University Hospital (35 controls). The time periods were on average 4 years apart. Collection of control serum samples was performed with the approval of the Ethics Committee of the Department of Obstetrics and Gynaecology, Helsinki University Hospital. All samples were stored at −25 °C and analysed simultaneously.

The mean ages of the patients and controls were 61.2 years (range 40.0–82.8 years) and 61.5 years (range 24.5–87.0 years), respectively. Clinical and histopathological characteristics are shown in Table 1.

Table 1 – Clinical characteristics of 79 patients with primary fallopian tube carcinoma (PFTC)

Parameter	*n*	(%)
Stage		
I	11	(14)
II	12	(15)
III	40	(51)
IV	15	(19)
No data	1	(1)
Grade		
1	7	(9)
2	20	(25)
3	45	(57)
No data	7	(9)
Histological type		
Serous	57	(72)
Anaplastic	13	(16)
Carcinosarcoma	5	(7)
Endometrioid	1	(1)
Clear cell	1	(1)
Unknown	2	(3)
Tumour size (cm)		
<2	7	(9)
2–5	14	(18)
5–10	19	(24)
>10	36	(45)
No data	3	(4)
Residual tumour size (cm)		
None	28	(35)
<0.5	2	(3)
0.5–1.0	1	(1)
1–2	4	(5)
>2	30	(38)
Peritoneal carcinosis	10	(13)
No data	4	(5)

2.1. *Chlamydia* serology

Chlamydia trachomatis- and *C. pneumoniae*-specific IgG antibodies were assayed by a micro-immunofluorescence method (MIF)[13] using pooled serovars (GFK, CJHI, BED) of *C. trachomatis* (Washington Research Foundation, Seattle, WA, United States of America (USA)) and serovar Kajaani 6 for *C. pneumoniae* as control antigens, and fluorescein isothiocyanate (FITC)-conjugated anti-human IgG (Kallestad, Chaska, MO, USA) as conjugate.[13] The serum samples were analysed at two-fold dilutions for *C. trachomatis* and at four-fold dilutions for *C. pneumoniae*. Titres of $\geqslant 16$ were considered positive for *C. trachomatis*. Titres of $\geqslant 32$ were considered positive for *C. pneumoniae*.

2.2. Statistical analysis

A statistical power of 80% was planned to detect a hypothesised difference at a two-tailed significance of $P < 0.05$. The power calculations were based on a hypothesised odds ratio (OR) of 2.8[8] and a prevalence of *C. trachomatis* antibodies of 14% in the general population.[14] Thus, 135 controls would be needed for the cases. Univariate and multivariate ORs with 95% confidence intervals (CIs) and two-sided *P*-values were estimated by conditional logistic regression.[15] Statistical calculations were performed using Stata 8.0 (Stata Corp, College Station, Tex) and SPSS 12.0 (SPSS Inc, Chicago, III) software.

3. Results

Seropositivity to the different *C. trachomatis* serovars and to *C. pneumoniae* in PFTC patients varied from 13.9% to 21.5%. In control subjects seropositivity varied from 10.3% to 21.8% (Table 2). The overall prevalence of *C. trachomatis* IgG antibodies to one or more serotype pools in PFTC patients and controls was 20% and 16%, respectively ($P = 0.42$). Serum IgG antibodies to the different *C. trachomatis* serovars or to *C. pneumoniae* were not associated with PFTC (Table 3). The presence of serum IgG antibodies to more than one serotype pool did not increase the risk of PFTC (Table 4). The study population was divided into age quintiles to study the effect of age on seropositivity, but again there was no correlation. However, patients with elevated *C. trachomatis* IgG titres to serotypes BED were younger than control subjects, 39 years versus 56 years ($P = 0.038$). When comparing PFTC patients and con-

Table 2 – Seropositivity to different *chlamydia trachomatis* serovars and to *chlamydia pneumoniae* in PFTC (N = 79) and control patients (N = 156)

	Cases, *n* (%)	Controls, *n* (%)	
C. trachomatis			
CJHI	13 (16)	17 (11)	$p = 0.2$
GFK	13 (16)	23 (15)	$p = 0.7$
BED	11 (14)	16 (10)	$p = 0.4$
C. pneumoniae	17 (21)	34 (22)	$p = 0.9$

Table 3 – Odds ratios calculated by conditional logistic regression analysis of PFTC associated with different *chlamydia trachomatis* serovars and with *chlamydia pneumoniae*

	Odds ratio	95% CI[a]
Chlamydia trachomatis		
CHIJ	1.6	0.7–3.5
BED	1.4	0.6–3.2
GFK	1.1	0.5–2.4
Chlamydia pneumoniae	1.0	0.5–1.9

a CI = Confidence interval.

trols, a trend towards elevated *C. trachomatis* IgG antibody titres to one or more serotype pools was seen among younger PFTC patients, whereas such trend was not seen among young controls, but this did not reach statistical significance ($P = 0.115$). Stage, histology or grade showed no association with seropositivity to *C. trachomatis* or *C. pneumoniae* and PFTC.

4. Discussion

This study is the first of an association between exposure to *C. trachomatis* and subsequent PFTC. The potential role of specific infectious agents as risk factors of PFTC is unknown. There have been some case reports of tuberculous salpingitis being a possible promoter of PFTC.[16] No evidence was found of the role of past history of chlamydial infection as a risk factor of PFTC. Thus, the results of this study were somewhat disappointing and unexpected. *C. trachomatis* is an intracellular bacterium and a major cause of salpingitis and PID. PID may lead to pyosalpinx, sactosalpinx, fallopian tube adhesions and obstruction, leading to ectopic pregnancy or tubal factor infertility.[17,18] One of the mechanisms by which chlamydia may be involved in carcinogenesis is through chronic persistent inflammation. Inflammation involves rapid cell division, DNA repair, oxidative stress, and high tissue concentrations of cytokines and prostaglandins, all of which can play a role in carcinogenesis.[19] Another important factor in carcinogenesis may be the anti-apoptotic effect of chlamydia.[20] Koskela and colleagues[8] have published sero-epidemiological evidence that infection with *C. trachomatis* confers an increased risk of subsequent development of invasive squamous cell carcinoma of the uterine cervix. The presence of serum IgG antibodies to serotype G increased the risk 6.6-fold. In addition, antibodies to more than one serotype tended to further increase the risk.[9] A number of investigators have found an elevated risk of ovarian carcinoma associated with a past history of PID.[10,11,19] Risch and Howe found an increased risk of ovarian carcinoma among women who had prior PID (OR 1.5).[11] The relationship between PID and ovarian carcinoma was strongest in women who had had PID at an early age, and in nulliparous or infertile women. The risk of ovarian cancer increased with the number of PID episodes. In contrast, Parazzini and colleagues found no link between ovarian carcinoma and history of PID.[21] However, cancer incidence correlations suggest common aetiological factors for cervical and ovarian cancer.[22] Furthermore, tubal ligation and hysterectomy protect against ovarian cancer, supporting the theory of ascending aetiological factors.[23] In the present study the risk of PFTC was not increased among those with chlamydial antibodies. This is difficult to explain. If there is an inflammatory agent ascending from the cervix to the ovaries, one would expect to see an association with fallopian tube carcinoma.

Data on the natural history and kinetics of *C. trachomatis* antibodies are limited. Puolakkainen and colleagues showed that *C. trachomatis* IgG antibodies measured by means of an indirect immunofluorescence technique persisted at stable levels in 43% of the women involved for up to 6 years; 43% of the women showed a decrease in IgG titres, and 13% showed an increase.[24] Chlamydial infections are rare among older women. In the present study, the mean age of the patients was 61.2 years. Chlamydial IgG antibodies were measured by MIF, which is considered the gold standard.[22] It is not known whether the negative results in the present study can be explained by decreasing serum chlamydial antibody titres. There are no studies on the possible protective effect of tubal ligation or hysterectomy on PFTC. If tubal ligation does not protect women from PFTC, this would support the negative results of the present study.

In conclusion, the presence of serum anti-chlamydial antibodies was not associated with PFTC. However, because chlamydial infection is common in young women and PFTC develops several decades later, one cannot exclude the possibility that it contributes to the development of PFTC.

Conflict of interest statement

None declared.

Table 4 – Risk by number of positive *C. trachomatis* serotype pools in PFTC patients and controls, univariate analysis

	Percent positive				
Number of serotype pools	Cases *n* (%)	Controls *n* (%)	Odds ratio	95%CI	*p*-value
0	63 (80)	131 (84)	1.0		
1	3 (4)	5 (3)	1.2	0.3–5.4	0.7
2	5 (6)	9 (6)	1.1	0.4–3.6	0.8
3	8 (10)	11 (7)	1.5	0.6–3.9	0.4
Total	79 (100)	156 (100)			

Acknowledgement

This study was supported by grants from Orion Research Foundation and Helsinki University Hospital, Finland.

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DOI: 10.1111/j.1471-0528.2006.01256.x
www.blackwellpublishing.com/bjog

Human papillomavirus infection and primary fallopian tube carcinoma: a seroepidemiological study

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Accepted 31 October 2006. Published OnlineEarly 19 February 2007.

Objective To evaluate the role of human papillomavirus (HPV) types 6, 11, 16, 18, 31 or 33 infection in primary fallopian tube carcinoma (PFTC).

Design A retrospective case–control study.

Setting Department of Obstetrics and Gynaecology, Helsinki University Hospital, Finland.

Population Seventy-eight consecutive women with PFTC diagnosed between 1985 and 2000 were studied. For each case, two healthy controls were selected.

Methods Serum immunoglobulin G antibodies to HPV types 6, 11, 16, 18, 31 and 33 were measured from women with PFTC and their healthy controls.

Main outcome measures Analysis of HPV 6, 11, 18, 31 and 33 seropositivity among women with PFTC and controls.

Results Seropositivity rates of non-oncogenic or oncogenic HPV types did not differ between cases and controls, odds ratios being 1.04–1.30 for oncogenic HPVs and 1.08–1.19 for non-oncogenic HPVs, similarly. We did not find any multiplicative joint effect in PFTC by antibodies to more than one oncogenic HPV type; neither did we find any antagonistic effect among women with antibodies to non-oncogenic and oncogenic HPV types.

Conclusions Our results do not suggest any link between PFTC and serological evidence for HPV infection.

Keywords *Chlamydia trachomatis*, herpes simplex virus type 2, human papillomavirus, primary fallopian tube carcinoma.

Please cite this paper as: Riska A, Finne P, Koskela P, Alfthan H, Jalkanen J, Lehtinen M, Sorvari T, Stenman U, Paavonen J, Leminen A. Human papillomavirus infection and primary fallopian tube carcinoma: a seroepidemiological study. BJOG 2007;114:425–429.

Introduction

Primary fallopian tube carcinoma (PFTC) is a rare but highly aggressive disease, comprising 0.1–1.1% of all female genital malignancies.[1] In Finland, the number of new cases of PFTC is rapidly increasing, now being seven-fold compared with 1953–1957.[2] Its aetiology is largely unknown but may be similar to that of ovarian carcinoma, as both arise from the müllerian duct. Studies on the absence or presence of human papillomavirus (HPV) DNA in carcinomatous epithelial ovarian tissue or endometrial tissue are conflicting.[3–7] HPV is a necessary cause of cervical cancer.[8] Antibodies to HPV virus-like particles (VLPs) correlate with the presence of HPV DNA in cervical neoplasia.[9] To the best of our knowledge, a possible link between HPV serology and PFTC has not been studied. One study has analysed 12 PFTC cases by comparative genomic hybridisation but revealed no presence of HPV genomes.[10] The objective of our study was to find out whether there is any serological evidence of the role of HPV infection in PFTC.

Materials and methods

Postoperative serum samples were collected and stored at –20°C until analysed from 78 consecutive women treated for PFTC at the Department of Obstetrics and Gynaecology, University Hospital, Helsinki, between 1985 and 2000. The study was approved by the Ethics Committee of the Department of Obstetrics and Gynaecology, Helsinki University Hospital. Patient data were retrieved by detailed chart review. The women had not received chemotherapy prior to surgery. Staging was performed according to the International Federation

of Obstetrics and Gynecology criteria. Pelvic and para-aortic lymphadenectomy was performed whenever possible. Stage, grade, histological findings, tumour size and size of the residual tumour were recorded. Serum samples were drawn at a median of 36 days (interquartile range 28–56 days) after primary surgery. For each case, two controls were selected from hospitalised women fulfilling the following criteria: matched age at serum sampling (±5 years) and no cancer diagnosis. For three cases, the age matching rule had to be violated, and controls with a larger age difference were included. Ninety postoperative control serum samples were collected from women attending Helsinki City Maternity Hospital, and 66 control serum samples were drawn from the Serum Bank of Helsinki University Hospital (12 archival serum samples from women operated for benign ovarian cysts, 19 samples from women seen for a benign colon disease and 35 archival serum samples from female hospital employees).

The mean age of the women and controls was 61.9 years (range 43.0–82.8 years) and 63.7 years (range 24.5–86.9 years), respectively. Selected tumour characteristics of the PFTCs are shown in Table 1.

Table 1. Selected tumour characteristics of the 78 PFTC cases

Parameter	*n* (%)
Stage	
I	10 (13)
II	12 (15)
III	40 (51)
IV	15 (19)
Unknown	1 (1)
Grade	
1	7 (9)
2	20 (26)
3	45 (58)
Unknown	6 (8)
Histological type	
Serous	57 (73)
Anaplastic	13 (17)
Carcinosarcoma	5 (6)
Endometrioid	1 (1)
Clear cell	1 (1)
Unknown	1 (1)
Tumour size (cm)	
<2	6 (8)
2–5	14 (18)
5–10	19 (24)
>10	36 (46)
Unknown	3 (4)
Residual tumour size (cm)	
None	27 (35)
<0.5	2 (2)
0.5–1.0	1 (1)
1–2	4 (5)
>2	30 (38)
Peritoneal carcinosis	10 (13)
Unknown	4 (5)

Laboratory methods

Immunoglobulin G (IgG) antibodies to oncogenic HPV types 16, 18, 31 and 33 and to non-oncogenic HPV types 6 and 11 were determined by the standard enzyme-linked immunosorbent assay (ELISA) method using HPV VLP capsid proteins as antigen and disrupted homologous capsids as the control antigen.[11,12] The assay included on each ELISA plate both positive and negative controls. Optical density (OD) values were normalised relative to the results of positive control (internal standard) sera. Cutoff levels were defined as the mean + 3 SD of OD values of sera from 38 virgin women. The cutoff levels for HPV 6, 11, 16, 18, 31 and 33 were 0.167, 0.142, 0.149, 0.125, 0.150 and 0.141 OD, respectively.

The HPV 16 VLPs were obtained from the Laboratory of Cellular Oncology, National Cancer Institute, National Institutes of Health, Bethesda, USA; types 11 and 6 VLPs (L1) were obtained from Merck Research Laboratories, West Point PA, USA; HPV 31 and 33 L1 VLPs, expressed in *Spodoptera frugiperda* insect cells, were kindly provided by Dr Kirnbauer, Vienna General Hospital, University of Vienna Medical School, Austria. The HPV 18 VLPs were obtained from GlaxoSmithKline Biologicals in Rixensart, Belgium. The reported sensitivity of the serologic assays for detection of antibodies to HPV VLPs has been 50–75%,[13,14] and the reported specificity is high.[15]

Chlamydia trachomatis IgG serology was measured by a peptide ELISA (*C. trachomatis* IgG EIA; ANILabsystems, Helsinki, Finland). This assay is based on synthetic peptides derived from the *C. trachomatis*-specific variable domain of major outer membrane protein.[16] The assay is an indirect solid-phase enzyme immunoassay with horseradish peroxidase as the marker enzyme. Signal to cutoff >1.4 was regarded as a positive result.

IgG antibodies to herpes simplex virus type 2 (HSV-2) were analysed by a commercial ELISA (Biokit SA, Barcelona, Spain) using purified baculovirus-expressed glycoprotein G2 as the antigen. The sample absorbance was divided by the cutoff value, and values >1.0 were regarded positive.[17] Both *C. trachomatis* and HSV-2 antibodies in serum are reliable markers of sexual behaviour.[11,18,19]

Statistical analysis

Differences in seropositivity between cases and controls were assessed using the chi-square test. Univariate and multivariate odds ratios (ORs) with 95% confidence intervals (CIs) were estimated by conditional logistic regression.[20] Two-sided *P* values below 0.05 were considered statistically significant. Statistical calculations were performed using Stata 8.0 (STATA Corp., College Station, TX, USA) and SPSS 12.0 software (SPSS Inc., Chicago, IL, USA).

Results

Seroprevalence rates of different HPV types did not differ between women with PFTC and controls (Table 2). In women with PFTC, the seropositivity for the non-oncogenic types (HPV 6 and 11) was 10 and 13%, respectively. The seropositivity rates for the oncogenic types HPV 16, 18, 31 and 33 were 22, 6, 14 and 10%, respectively. In the control subjects, the corresponding seropositivity rates to HPV 6 and 11 were 10 and 11% and to HPV 16, 18, 31 and 33 were 21, 5, 13 and 11%, respectively. The seropositivity rates to more than one HPV types were not different between cases and controls.

The OR of PFTC for one of the oncogenic HPV types was 0.96 (95% CI 0.46–2.02) in the absence of HPV 6/11 antibodies and 0.57 (95% CI 0.11–2.85) in the presence of HPV 6/11 antibodies. When there were antibodies to more than one oncogenic HPV type, the OR was 0.88 (95% CI 0.32–2.46) in the absence of HPV 6/11 antibodies and 1.44 (95% CI 0.37–5.61) in the presence of HPV 6/11 antibodies. The analyses were adjusted for HSV-2 and *C. trachomatis* antibodies (Table 3). All HPV-specific risk estimates of PFTC were non-significant (Table 4).

Table 2. Seropositivity to different HPV types, *C. trachomatis* and HSV-2 in women with PFTC and in controls

	Cases, $n = 78$ *n* (%)	Controls, $n = 156$ *n* (%)	*P* value
HPV			
HPV 6	8 (10)	15 (10)	0.88
HPV 11	10 (13)	17 (11)	0.66
HPV 16	17 (22)	33 (21)	0.91
HPV 18	5 (6)	8 (5)	0.69
HPV 31	11 (14)	21 (13)	0.89
HPV 33	8 (10)	17 (11)	0.88
C. trachomatis	14 (18)	28 (18)	0.90
HSV-2	19 (24)	34 (22)	0.66

Discussion

We found no evidence of the role of HPV, *C. trachomatis* or HSV-2 infection in PFTC. HPV causes cervical carcinoma,[21] and it has also been linked to vulval,[22] vaginal[23] and anal carcinomas.[24] Kaufman *et al.*[25] identified HPV DNA in advanced epithelial ovarian carcinoma tissue in 10 of 12 women, but Chen *et al.*[4] could not confirm these results, and later studies have also given conflicting results.[3–5,7,25–27] Fewer studies have been conducted on endometrial malignancies,[3,5,26–28] and the results are even more inconsistent. Studies have suggested that HPV could ascend up to the ovaries and fallopian tubes by sperm.[4] However, HPV may only be a 'passenger', and neither endometrium[28] nor fallopian tube epithelium may support HPV replication.

Although molecular methods are more sensitive, serological assays are useful to show associations in epidemiological studies. There is only one study where HPV DNA expression in PFTC has been evaluated.[10] The investigators did not find HPV DNA in women with PFTC, which is in accordance with our results.

We measured antibodies to HPV VLPs as markers of exposure to HPV. In women testing positive for HPV 16, 18 or 33 DNA in cervical samples, serum antibody response to HPV capsids of the corresponding HPV type has been found among 65, 69 and 75%, respectively.[14] This may lower the possibilities in detecting very marginally raised levels of serum HPV antibodies. It is known that in women, seroconversion against HPV VLPs occurs within a few months following acquisition of HPV 16 DNA and that serum antibody levels remain stable over long periods of time.[15] In our study, the HPV 16 seroprevalence rates were 22% in women with PFTC and 21% in controls. In other studies, the prevalence of HPV antibodies in control subjects has varied between 10 and 20%.[29]

In Western countries, the incidence of PFTC has increased during the past decades.[2,30] In Finland, the incidence has increased especially among women in higher social classes and among those living in urban areas. It would be tempting

Table 3. Adjusted ORs for PFTC by seropositivity to high-risk HPV types or low-risk HPV types

Seropositivity for one or more of HPV 16/18/31/33	Seropositivity for HPV 6/11	Cases, *n*	Controls, *n*	OR (95% CI)*
0	No	47	91	1.00 (reference group)
0	Yes	5	12	0.80 (0.27–2.42)
1	No	14	28	0.96 (0.4–2.02)
1	Yes	2	7	0.57 (0.11–2.85)
2–4	No	6	13	0.88 (0.32–2.46)
2–4	Yes	4	5	1.44 (0.37–5.61)

*Adjusted for seropositivity to HSV-2 and *C. trachomatis*.

Table 4. ORs for HPV, HSV-2 or *C. trachomatis* in PFTC by conditional logistic regression analysis

	OR	95% CI	*P*
HPV 6	1.08	0.42–2.79	0.871
HPV 11	1.19	0.53–2.69	0.672
HPV 16	1.04	0.53–2.06	0.907
HPV 18	1.30	0.38–4.45	0.671
HPV 31	1.05	0.49–2.23	0.897
HPV 33	0.93	0.38–2.29	0.880
HSV-2	1.14	0.61–2.12	0.67
C. trachomatis	0.96	0.48–1.92	0.906

to speculate that the increase is associated with increased prevalence of gynaecological infections. Infertility, nulliparity and age of the women have also been considered as risk factors.[31] The aetiological factors have not been clearly defined, but chronic inflammation has been implicated. In one study, 22% of the women with PFTC had history of salpingitis,[32] and tuberculous salpingitis has also been suggested to be a possible promoter of PFTC.[33] A number of investigators have found an elevated risk of ovarian carcinoma associated with a history of pelvic inflammatory disease, but we did not find any association between serum antibodies to *C. trachomatis* and PFTC.[34]

In conclusion, our retrospective seroepidemiologic case–control study is the first to examine a possible link between serum antibodies to HPV and PFTC. The results do not suggest that HPV contributes to the development of PFTC.

Acknowledgements

This study was supported by the Helsinki University Hospital Research Funds, Research Foundation of Orion Corporation, the Finnish Cancer Foundation, the Finnish Medical Foundation and the Schering Research Foundation. Special thanks are due to Mrs Taina Grönholm and to Mrs Anne Ahmanheimo for helping to find serum samples. ■

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Int. J. Cancer: **120,** 1351–1354 (2007)

Parity, tubal sterilization, hysterectomy and risk of primary fallopian tube carcinoma in Finland, 1975–2004

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We studied the possible relationship among parity, female sterilization, hysterectomy and the risk of primary fallopian tube carcinoma (PFTC) in a case–control study in Finland in cases occurring between 1975 and 2004. A total of 573 PFTC cases were identified from the Finnish Cancer Registry, and10 age-matched controls per case were randomly selected from the Finnish Central Population Registry. In multivariate analysis (including 189 PFTC cases and 1764 controls) parity was protective: the odds ratio (OR) for 1–2 deliveries was 0.63 (95% CI 0.44–0.91) and for ≥3 deliveries, 0.32 (95% CI 0.19–0.52). The OR for sterilization was 0.74 (95% CI 0.42–1.30) and for hysterectomy 1.27 (95% CI 0.73–2.21). Our findings suggest a possible hormonal background as regards the development of PFTC.
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Key words: PFTC; tubal sterilization; hysterectomy; parity

Primary fallopian tube carcinoma (PFTC) is a very rare but aggressive disease, reported to comprise 0.1%–1.1% of all female genital malignancies in Western countries.[1] In Finland the age-adjusted incidence has been rising during the last few decades and is now 0.5/100,000 women.[2] About one third of patients with PFTC will be alive 5 years after diagnosis.[3] Environmental and lifestyle factors may play important roles as regards the risk of PFTC.[2]

There are several studies on the protective effect of sterilization (tubal ligation) on the risk of ovarian cancer.[4–6] A similar effect of hysterectomy on ovarian cancer has also been observed.[4,5,7] There are no studies on the effect of these procedures on PFTC. There have been various theories for these observations concerning ovarian cancer,[8] including a screening effect,[9] a decrease in uterine growth factors that could be involved in ovarian cancer development,[10] the effect of retrograde menstruation,[11] changes in blood flow to the ovaries,[5] which could have an influence on plasma hormone levels and ovarian function, and blockage of exposure to ascending environmental agents, such as talc.[12] Parity (up to 5 deliveries) is protective as regards ovarian cancer but age at first birth has no major impact.[13] In endometrial cancer, stronger protection with increasing number of deliveries and with increasing age at first birth has been detected.[14] Because both the ovaries and fallopian tubes develop from the Müllerian ducts, they could behave similarly in some respects.

Finland is an industrialized country with 5.3 million inhabitants, most of whom live in urban communities. The country has an effective healthcare system, 75% of which is publicly financed, and the user charges are relatively low. The nationwide population-based Finnish Cancer Registry, the Hospital Discharge Registry (HILMO) and the Finnish Central Population Registry (CPR) allowed us to carry out a reliable case–control study on the effect of parity, sterilization, hysterectomy and previous cancer on PFTC in Finland from 1975 to 2004.

Material and methods

We selected from the Finnish Cancer Registry all women reported to have had PFTC in 1975–2004 ($n = 573$). The Registry obtains information from hospitals and other institutions with in-patient beds, general practitioners, pathology and cytology laboratories, and from death certificates with cancer diagnoses. More than 99% of all cancer cases have been reported to the Registry since 1953.[15] In the 1990s, about 95% of the cases were microscopically confirmed, and about 1% of the cases were based on death certificate data only.[16]

The CPR has covered information on all residents of Finland since 1967, and their relatives since 1973.[17] Ten age-matched female controls (±1 month) ($n = 5473$) were selected from the CPR for each PFTC patient. The control subjects had to be alive at the time when diagnosis of the PFTC patient was completed. The dates of birth of children of PFTC patients and control subjects were collected from the CPR.

The CPR administers the Finnish system of unique identifiers (IDs). It was started in 1964, and by 1967 all Finnish citizens and permanent residents had received their own ID. These IDs are used in practically all Finnish registries, and they were used as linkage keys to combine information from various registries in this study.

The sterilization, hysterectomy and salpingectomy data were obtained from HILMO, which has operated since 1967 and is maintained by STAKES, the National Research and Development Centre for Welfare and Health.[17] The Registry contains summary information on patients discharged from all public and private hospitals. Virtually all discharges from inpatient wards are registered, and the accuracy of the main diagnosis is more than 95% at the three-digit level when comparing the principal diagnosis in HILMO and the diagnosis in medical records at discharge.[18] Recording of surgical events started in 1986; the completeness and accuracy of recording is reasonably good.[19] During the period 1986–1996 surgical procedures were recorded according to the classification of surgical procedures issued by the Finnish Hospital League,[20] and from 1997 according to the Nordic Classification of Surgical Procedures introduced in 1996, also covering day surgery episodes.[21]

Reliable data on sterilizations were available from 1975, and on the events of hysterectomies and salphingectomies from 1986. Only events occurring more than half a year before the PFTC diagnoses (or the corresponding day for controls) were included. The numbers of children were derived by using data obtained from the CPR, which is able to reliably identify live-born children of women born after the mid-1930s. Age at first delivery could also be calculated by using the date of birth of the oldest child of each mother.

It can be expected that the risk of PFTC decreases if salpingectomy has been performed. Therefore, we excluded all 8 women with an operation code for unilateral or bilateral salpingectomy before the day of PFTC diagnosis. After this exclusion, 565 PFTC

Grant sponsors: Helsinki University Hospital Research Funds, Research Foundation of Orion Corporation, Finnish Cancer Foundation, Finnish Medical Foundation, Schering Research Foundation, Finnish Cultural Foundation.

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Received 12 June 2006; Accepted after revision 20 October 2006
DOI 10.1002/ijc.22491
Published online 27 December 2006 in Wiley InterScience (www.interscience.wiley.com).

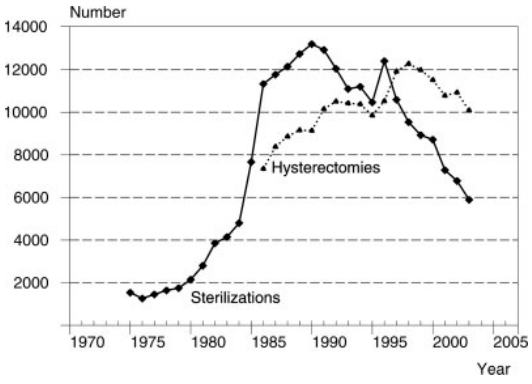

FIGURE 1 – The annual number of registered sterilizations and hysterectomies in Finland, 1975–2003.

patients and 5473 control women remained. Since sterilization data were not available until 1975, only the women born after 1925 were included for sterilization analyses (375 cases and 3587 controls), assuming that a sterilization procedure is no longer necessary for women aged 50 years or more. Hysterectomy data were available from 1986. Women born before 1936 were dropped from the hysterectomy analyses, to be certain that all hysterectomies during the analysis period would be registered (189 cases and 1764 controls remained in the analysis). For parity and multivariate analyses the same restrictions as for hysterectomy analyses were used, to be certain that data concerning children were available from the CPR.

In Finland, from 1975 to 2003, a total of 222,068 sterilizations were performed, and from 1986 to 2003, 184,212 hysterectomies were performed. From 1975 until 1990 the number of sterilizations per year increased, but since then it has decreased every year. The rapid increase of sterilizations during the time period 1984–1987 was a result of changes in the sterilization legislation in 1985, making the law more liberal and family planning-oriented. The frequency of hysterectomies per year rose steadily from 1986 (7325 hysterectomies) to 1998, but later the tendency has been decreasing (Fig. 1).

The Ministry of Social Affairs and Health gave permission to use the confidential register data in scientific research, after consulting the register keepers and the data protection authority.

Analyses

The risk ratios in terms of odds ratios (ORs) were calculated, with 95% confidence intervals (CIs), by using univariate and multivariate conditional logistic regression for 1:m matched sets.[22] The statistical software packages Survo MM (www.survo.fi) and Stata release 8 (www.stata.com) were used in data processing and analyses.

Results

The strongest protective factor as regards PFTC was parity: parous women had an OR of 0.54 (95% CI 0.39–0.75) when compared with nulliparous women in the univariate analysis. An increasing number of deliveries resulted in stronger protection against PFTC and the older age at first birth was also protective (Table I).

Altogether, 375 PFTC patients and 3587 controls were included in the analysis of sterilization effects. Fifteen PFTC patients and 230 controls had undergone sterilization. In the univariate analysis, there was a statistically borderline-significant decrease in the risk of PFTC among women who had undergone sterilization (OR 0.58, 95% CI 0.33–1.00) (Table I). The protective effect was stronger among those who were younger at the time of sterilization.

There were 189 PFTC patients and 1764 control women, all born after 1935, included in the analysis related to hysterectomy. The univariate OR as regards hysterectomy was 1.14 (95% CI 0.66–1.98) (Table I).

Twenty-three cases of previous breast cancer (50% of all previous cancers) among patients with PFTC and 135 cases among the controls were detected. The OR for PFTC after previous breast cancer was 1.69 (95% CI 1.08–2.67) and after other cancers, 1.23 (95% CI 0.79–1.91).

Multivariate analysis

The multivariate analysis included women born after 1935. When parity, sterilization, hysterectomy and previous breast cancer were included in the same model, parity was the only statistically significant protective factor as regards PFTC. The protection became stronger with increasing number of deliveries: OR for 1–2 deliveries 0.63, 95% CI 0.44–0.91; and for $\geq$3 deliveries 0.32, 95% CI 0.19–0.52 (Table II). Sterilization nonsignificantly reduced the risk of PFTC (OR 0.74, 95% CI 0.42–1.30). Hysterectomy was more common among PFTC patients than their controls (OR 1.27, 95% CI 0.73–2.21). Previous breast cancer increased the risk, but nonsignificantly (OR 1.63, 95% CI 0.70–3.77).

Discussion

Our study is the first in which the effects of parity, sterilization and hysterectomy on PFTC have been evaluated. It is well known that parity reduces the risks of ovarian, endometrial and breast cancer.[13,14,23] In our material, parity was strongly protective and a higher number of deliveries increased the protection. An older age at first birth was also protective. A similar beneficial effect of older age at first birth has been detected in endometrial cancer,[14,24] but the influence of age at first birth on ovarian cancer is unclear. Some investigators have reported an increase in risk as regards older age at first birth[25] and others an increased risk associated with younger age at first birth.[25] A recent Finnish report revealed no correlation between age at first birth and ovarian cancer risk.[13] There are several theories concerning the protective effect of pregnancies. The results of animal studies suggest that progestagen-induced apoptosis of transformed ovarian surface epithelial cells may underlie the observed protective effect of pregnancy on the risk of ovarian cancer.[26] The endosalpingeal lining of the fallopian tube is hormonally reactive and the higher levels of progestagens during pregnancy could lower the risk of PFTC by inducing apoptosis of transformed epithelial cells.

We found borderline-significant protection against PFTC after sterilization. This result is in accordance with the results of several studies indicating a protective effect of sterilization on ovarian carcinoma.[6,11,27] The theory of blockage of ascending carcinogenic agents such as talc,[11,28] contraceptive foams or gels,[29] viruses[30] or uterine growth factors[31,32] by sterilization has largely been studied in connection with ovarian cancer, but factors other than ascending agents may be required to explain the protective effect of sterilization on the risk of PFTC.

Hysterectomy did not give protection against PFTC; rather it increased the risk, but insignificantly. The marginally increased risk of PFTC among hysterectomized women could be based on hormonal features, such as raised levels of FSH. High levels of gonadotrophins, mainly FSH, have been hypothesized to stimulate malignant transformation of ovarian epithelial cells[31,33,34] and also fallopian tube epithelium *in vitro*.[35] Elevated concentrations of gonadotrophins could induce vascular endothelial growth factor expression and that way accelerate tumour growth, at least in ovarian epithelial cells.[36]

In our analyses previous breast cancer was not a risk factor for PFTC, but a positive trend was seen. Early menarche and late

TABLE I – UNIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH PFTC

	Cases, *n* (%)	Controls, *n* (%)	OR[1]	95% CI[2]
All women	565	5473		
No previous cancer	519 (91.9)	5151 (94.1)	1.00	Reference
Previous cancer	46 (8.1)	322 (5.9)	1.42	1.03–1.98
Type of previous cancer				
No previous cancer	519	5151	1.00	Reference
Breast cancer	23	135	1.69	1.08–2.67
Other cancer	23	187	1.23	0.79–1.91
Women born 1925+	375	3587		
No sterilization	360 (96.0)	3357 (93.6)	1.00	Reference
Sterilization	15 (4.0)	230 (6.4)	0.58	0.33–1.00
Age at sterilization				
No sterilization	360	3357	1.00	Reference
<40 years	4	115	0.30	0.11–0.84
≥40 years	11	115	0.85	0.45–1.61
Time since sterilization				
No sterilization	360	3357	1.00	Reference
<10 years	11	108	0.93	0.48–1.81
≥10 years	4	122	0.29	0.11–0.79
Women born 1936+	189	1764		
No hysterectomy	173 (91.5)	1633 (92.6)	1.00	Reference
Hysterectomy	16 (8.5)	131 (7.4)	1.14	0.66–1.98
Age at hysterectomy				
No hysterectomy	173	1633	1.00	Reference
<45 years	9	63	1.36	0.66–2.79
≥45 years	7	68	0.95	0.42–2.12
Time since hysterectomy				
No hysterectomy	173	1633	1.00	Reference
<10 years	9	102	0.84	0.41–1.69
≥10 years	7	29	2.19	0.93–5.16
No deliveries	51 (27.0)	280 (15.9)	1.00	Reference
Women with deliveries	138 (73.0)	1484 (84.1)	0.54	0.39–0.75
Age at first birth				
No deliveries	51	280	1.00	Reference
<35 years	135	1428	0.52	0.37–0.74
≥35 years	3	56	0.30	0.09–1.00
Parity				
No deliveries	51	280	1.00	Reference
1–2 deliveries	111	994	0.62	0.44–0.89
3 or more deliveries	27	490	0.30	0.18–0.49

[1]Odds ratios.–[2]CI, confidence interval.

TABLE II – ODDS RATIOS (OR) FROM MULTIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH PFTC (189 CASES, 1764 CONTROLS)

	Cases	Controls	OR	95% CI[1]
Parity				
No deliveries	51	280	1.00	Reference
1–2 deliveries	111	994	0.63	0.44–0.91
3 or more deliveries	27	490	0.32	0.19–0.52
No sterilization	174	1539	1.00	Reference
Sterilization	15	225	0.74	0.42–1.30
No hysterectomy	173	1633	1.00	Reference
Hysterectomy	16	131	1.27	0.73–2.21
No previous breast cancer	182	1727	1.00	Reference
Previous breast cancer	7	37	1.63	0.70–3.77

[1]CI, confidence interval.

menopause may increase the risk of breast cancer. Long-term cyclic exposure to ovarian hormones is a risk factor for this cancer and the long-term effect of a full-term pregnancy is protective.[37] This is in line with our results. Nulliparity is a risk factor for PFTC and for breast cancer. There are studies indicating clustering of breast cancers and PFTC in the same patients.[38,39] Several investigators have detected a higher prevalence of *BRCA1* and *BRCA2* mutation among PFTC patients than in the general population.[40–43] During surgery, prophylactic bilateral salpingectomy has been proposed for women at risk of familial breast-ovarian cancer,[44] especially those carrying *BRCA1* mutations.[45] Our results point in the same direction.

Our nationwide, population-based material represents the largest case–control study concerning PFTC. The number of controls per cancer patient is large, allowing maximal possible power in our analyses. In Finland, the Cancer Registry has been functioning since 1953 with coverage of 99% of all cancer cases, and coverage and accuracy of recorded surgical procedures in the Hospital Discharge Registry is also good. Hence, we can exclude selection bias and major misclassification information bias related to the registration of conditions and interventions among hospital patients.

PFTC is a rare malignancy. Our findings suggest a possible hormonal background associated with PFTC, especially a pregnancy-related background. Sterilization may reduce the risk of PFTC, while hysterectomy seems not to offer any protection. Further investigations are needed to clarify the role of hormones, especially the importance of pregnancy hormones, in the pathogenesis of PFTC.

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Int. J. Cancer: **120,** 2047–2051 (2007)

SHORT REPORT

Second primary malignancies in females with primary fallopian tube cancer

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Primary fallopian tube cancer (PFTC) is a rare disease, and its aetiological factors are poorly understood. Studies on PFTC in the setting of 2nd primary malignant neoplasms can provide clues on aetiology and also define the possible side effects of different treatment modalities for PFTC. A cohort of 2,084 cases with first PFTC was extracted from the data from 13 cancer registries from Europe, Canada, Australia and Singapore and followed for second primary cancers within the period 1943–2000. Standardized incidence ratios (SIRs) were calculated and Poisson regression analyses were done to find out the RRs related to age at, period of and time since the PFTC diagnosis. There were 118 cancer cases observed after first PFTC (SIR 1.4, 95%CI 1.1–1.6). Elevated SIRs were seen for colorectal cancer (1.7, 95%CI 1.0–2.6), for breast cancer (1.5, 95%CI 1.1–2.2), for bladder cancer (2.8, 95%CI 1.0–6.0), for lung cancer (1.8, 95% CI 0.9–3.2) and for nonlymphoid leukaemia (3.7, 95%CI 1.0–9.4). Significant risk increases were detected for colorectal cancer during the 2nd to 5th year after the first PFTC diagnosis, for breast cancer in follow-up 10+ and for nonlymphoid leukaemia during the 2nd to 10th year. The clustering of cancers of the lung and bladder in PFTC patients may suggest shared smoking aetiology. The excess of colorectal and breast cancers after PFTC may indicate a genetic aetiology.

Key words: primary fallopian tube cancer; second primary cancer; multi-centre cohort study

Primary fallopian tube cancer (PFTC) is a rare disease, contributing 0.3%–1.6% of female genital tract malignancies in Western countries.[1–3] Studies from the United States indicated an incidence rate of 0.4 per 100,000 in the 1980s; with the rate being higher in Caucasian women including Hispanics than in African Americans.[4] In Finland, the age-adjusted incidence rate increased from 0.1/100,000 in 1953–1957 to 0.5/100,000 in 1993–1997.[3] In Denmark, the incidence rate during a 5-year period around 1980 was 0.3/100,000.[5] The 5-year survival rate has varied between 22 and 57% over times and regions.[5–8]

Little is known about aetiology of PFTC. More than 90% of the cases are serous adenocarcinomas and the histological appearance resembles that of ovarian serous carcinomas.[1,4,9] Fallopian tube is a hormone sensitive organ. The epithelial cells of fallopian tube undergo changes during the menstrual cycle in response to changes in hormonal levels, particularly oestrogen. PFTC has been generally treated as ovarian cancer since both tumors have similar histologies and biological behavior.[10] Studies have reported clustering of breast cancers and PFTC in same patients.[2,11,12] There are also several findings on higher BRCA1 and BRCA2 mutation prevalence among PFTC patients than in average healthy population.[13–16]

The present investigation is a unique multi-centre study including cancer data from 13 population-based cancer registries in Europe, Australia, Canada and Singapore.

Material and methods

This study is part of an international multi-centre study of second primary cancers coordinated by the International Agency for Research on Cancer (IARC) including data from 13 cancer registries in Europe, Australia, Canada and Singapore that have been in operation for at least 25 years (Table I). Details of data handling and standardization between the 13 participating registries have been described elsewhere.[17,18] Coding of multiple primaries in the cancer registries has followed a common set

Grant sponsors: Finnish Cultural Foundation, The Finnish Cancer Foundation, The Finnish Medical Foundation, Lilly Foundation, The National Cancer Institute; Grant number: R03 CA101442-02.
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Received 14 November 2006; Accepted after revision 24 November 2006
DOI 10.1002/ijc.22562
Published online 31 January 2007 in Wiley InterScience (www.interscience.wiley.com).

TABLE I – CHARACTERISTICS OF THE COHORT OF FIRST PRIMARY FALLOPIAN TUBE CANCER CASES (PFTC) EXTRACTED FROM 13 CANCER REGISTRIES, AND NUMBERS OF SECOND PRIMARY CANCERS FOLLOWING PFTC BY DECEMBER 31, 2000

Characteristics	PFTC		Second primary cancer	
	n	%	*n*	Cumulative incidence of second primary cancers (%)
Age at PFTC diagnosis				
21–49	394	18.9	26	6.6
50–59	601	28.8	39	6.5
60–92	1089	52.3	53	4.9
Calendar period of PFTC diagnosis				
<1975	501	24.0	46	9.2
1975–1983	425	20.4	31	7.3
1984–1990	479	23.0	24	5.0
1991+	679	32.6	17	2.5
Time since PFTC diagnosis (full years)				
<1	472	22.6	15	3.2
1−4	972	46.6	42	4.3
5–9	297	14.2	17	5.7
10+	343	16.4	44	12.8
Cancer Registry				
Australia, New South Wales	72	3.4	7	9.7
Canada, British Columbia	112	5.4	12	10.7
Canada, Manitoba	40	1.9	4	10.0
Canada, Saskatchewan	30	1.4	1	3.3
Denmark	505	24.2	34	6.7
Finland	464	22.2	16	3.4
Iceland	12	0.6	0	0.0
Norway	277	13.3	12	4.4
Singapore	26	1.2	3	11.5
Slovenia	100	4.8	8	8.0
Spain, Saragoza	11	0.5	0	0.0
Sweden	378	18.1	20	5.3
UK, Scotland	57	2.7	1	1.7
Total	2084	100	118	5.7

of rules proposed by the International Association of Cancer Registries (IACR) and the IARC.[19] This was possible as all participating cancer registries currently use the IARC/IACR rules or a local set of more extensive or detailed rules. According to the rules, a primary cancer is one which originates in a primary site or tissue and is thus neither an extension, nor a recurrence nor a metastasis. Only one tumor shall be recognized as arising in an organ or pair of organs or tissue unless the histology is different. Second tumors occurring in the fallopian tube were however not analyzed, because rules were not compatible between registries or over time. Cancers of the brain and nervous system, bladder cancer and nonmelanoma skin cancer have been registered differently in the various registries. In the present study, we followed the same rules as applied in the series of volumes of Cancer Incidence in 5 Continents.[20]

The data from the 13 cancer registries were checked carefully for inconsistencies and missing information, with verification provided by the local registry when required. A small proportion of subjects (0.06%) were excluded because of remaining missing or inconsistent information. Furthermore, patients for whom the first primary cancer diagnosis and death were recorded at the same time or who had 2 first primary cancers recorded simultaneously (same dates of diagnosis) were excluded (8%). After these exclusions, there were 2,084 women with a first PFTC. No treatment data for PFTC were available.

All cases of PFTC were followed up for second primary cancer from date of first diagnosis (1943–2000) to date of second primary cancer (1943–2000), date of death, date of migration or end of follow-up (1992–2000). The number of second primary cancers observed was compared with the expected number of cancers calculated from accumulated person-years and rates among females of first PFTC specific for each registry and 5-year age and calendar-periods. The standardized incidence ratios (SIRs) were stratified for time since PFTC diagnosis (<1year, 1–4, 5–9 and 10+ years after the diagnosis first PFTC), for calendar-period of PFTC (<1975, 1975+) and for age at PFTC diagnosis (21–49 years, 50–59 years, 60–92 years). A Poisson regression analysis was done for selected cancer sites to quantify the independent risk ratios (RR) related to each variable.

Results

The study population of 2,084 women with a first PFTC contributed 11,047 person-years of follow-up (median 2.5, mean 5.3, maximum 49.6 years). At the time of the PFTC diagnosis, 52% of women were 60+ years-old, 24% were diagnosed before 1975 (Table I). The majority of cases were from Europe (87%). The proportion of patients having a second primary cancer after PFTC during the follow-up was 5.7% (Table I).

The SIR of second primary cancer in all sites combined after a PFTC was 1.4 (95% CI = 1.1–1.6) (Table II). Elevated risks were seen for colorectal cancer (SIR 1.7, 95% CI 1.0–2.6), breast cancer (SIR 1.5, 95% CI 1.1–2.2), bladder cancer (SIR 2.8, 95% CI 1.0–6.0), nonlymphoid leukaemia (SIR 3.7, 95% 1.0–9.4) and lung cancer (SIR 1.8, 95% CI 0.9–3.2). There were no second cancers with significantly decreased risk.

The SIR for second cancer (all sites combined) was highest if the time since PFTC diagnosis was 10+ years, age at PFTC diagnosis <60 years, or the year of PFTC diagnosis <1984 (Table III).

For breast cancer, a significantly elevated SIR of 2.3 (95% CI 1.2–3.8) was seen over 10 years after the diagnosis of PFTC (Table III). Also in the multivariate analysis there was an indication of an increase of breast cancer cases 10+ years after the PFTC as compared with shorter follow-up times. The age or calendar period of the diagnosis had no effect.

For colorectal cancer, a significant increase (SIR 2.1, 95% CI 1.3–4.9) was detected during the 2nd to 5th year after PFTC diagnosis (Table III). If the PFTC was diagnosed before the age of 60 years, the relative risk of colorectal cancer tended to be high

TABLE II – OBSERVED NUMBERS OF SUBSEQUENT PRIMARY CANCER CASES, STANDARDIZED INCIDENCE RATIOS (SIR) AND 95% CONFIDENCE INTERVALS (CI) AMONG 2,084 WOMEN WITH A FIRST PRIMARY FALLOPIAN TUBE CANCER (PFTC)

Cancer site (ICD-9)	Observed	SIR	95% CI
All malignant (140–208)	118	1.4	1.1–1.6
Oral cavity, pharynx (140–149)	2	1.5	0.2–5.6
Oesophagus (150)	1	1.3	0.0–7.3
Stomach (151)	3	0.7	0.2–2.2
Small intestine (152)	1	3.5	0.1–20
Colorectal (153, 154)	20	1.7	1.0–2.6
Colon (153)	13	1.7	0.9–2.9
Rectum (154)	7	1.7	0.7–3.5
Liver (155.0, 155.1)	0	–	0–5.0
Gallbladder, bile ducts (156)	3	1.9	0.4–5.5
Pancreas (157)	4	1.3	0.4–3.3
Peritoneum (158)	0	–	0–28
Lung (162)	11	1.8	0.9–3.2
Bone (170)	0	–	0–34
Soft tissue sarcoma (171)	1	2.5	0.1–14
Melanoma of skin (172)	1	0.4	0.0–2.5
Other neoplasm of skin (173)	9	1.5	0.7–2.9
Breast (174)	33	1.5	1.1–2.2
Cervix uteri (180)	2	0.7	0.1–2.4
Corpus uteri (182)	2	0.3	0.0–1.3
Other female genital (179, 184)	2	1.8	0.2–6.7
Bladder (188, 189.3–4)	6	2.8	1.0–6.0
Kidney (189.0–2, 189.5–9)	2	0.9	0.1–3.1
Brain, nervous system (191–192)	0	–	0–3.3
Thyroid gland (193)	2	2.3	0.3–8.3
Hodgkin's disease (201)	0	–	0–15
Non-Hodgkin's lymphoma (200, 202)	2	0.9	0.1–3.1
Multiple myeloma (203)	1	0.8	0.0–4.4
Leukaemia (204–208)	5	2.6	0.8–6.0
Lymphoid (204)	1	1.2	0.0–6.5
Nonlymphoid (205–208)	4	3.7	1.0–9.4
Others	5	1.2	0.4–2.7

TABLE III – OBSERVED NUMBERS (OBS) AND STANDARDIZED INCIDENCE RATIOS (SIR) FOR SECOND PRIMARY CANCER AMONG 2,084 WOMEN WITH A FIRST PFTC, BY AGE AND CALENDAR PERIOD AT PFTC DIAGNOSIS AND BY TIME SINCE PFTC DIAGNOSIS

Factor	Cancer site (ICD-9)								
	All malignant (140–208)			Female breast (174)			Colorectal (153,154)		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Age at PFTC diagnosis									
<50	26	1.6	1.0–2.4	7	1.4	0.6–2.8	4	2.3	0.6–5.9
50–59	39	1.5	1.1–2.1	12	1.8	0.9–3.0	7	2.2	0.9–4.5
>60	53	1.2	0.9–1.6	14	1.4	0.8–2.4	9	1.3	0.6–2.5
Calendar period of PFTC diagnosis									
<1975	46	1.5	1.1–2.0	11	1.6	0.8–2.9	8	1.8	0.8–3.6
1975–1983	31	1.5	1.0–2.1	9	1.8	0.8–3.4	5	1.7	0.6–4.0
1984–1990	24	1.2	0.8–1.8	7	1.3	0.5–2.7	5	2.0	0.6–4.6
1991+	17	1.1	0.6–1.7	6	1.3	0.5–2.9	2	1.0	0.1–3.5
Time since PFTC diagnosis (years)									
<1	15	1.2	0.7–2.0	5	1.5	0.5–3.4	2	1.2	0.2–4.4
1–4	42	1.5	1.1–2.0	9	1.2	0.5–2.3	10	2.7	1.3–4.9
5–9	17	1.0	0.6–1.5	5	1.1	0.4–2.6	2	0.8	0.1–3.0
10+	44	1.6	1.2–2.2	14	2.3	1.2–3.8	6	1.5	0.5–3.2

(combined SIR of age categories <50 and 50–59 years 2.2, 95% CI 1.1–4.0). Multivariate analysis gave essentially the same result: the RR 1–4 years after the PFTC was 3.3 as compared with follow-up 10+ years (95% CI 1.0–11) and the RR related to PFTC diagnosed in ages 60+ years or in 1991+ as compared with younger ages or earlier calendar periods, respectively.

In multivariate analysis for the remaining cancers combined (after exclusion of breast and colorectal cancers) there was some indication of a higher risk related to PFTC diagnoses before 1984. Elevated risks after first PFTC were also detected for nonlymphoid leukaemia during the 2nd to 10th year after PFTC diagnosis (4 cases, SIR 6.9, 95% CI 1.9–17.8) and for bladder cancer in follow-up 5+ years (7 cases, SIR 4.2, 95% CI 1.4–9.7). There were 2 cases of endometrial cancer and 2 cases of cervical cancer all of them diagnosed within 1 year after the PFTC.

Discussion

The number of fallopian tube cancer survivors has increased because of advances in earlier detection, treatment and supportive care. Therefore the risk of second primary cancers has become clinically more relevant. Our study—the largest one on second primary cancers after the first PFTC reported so far—showed that women with first PFTC had a 40% increased risk of developing a new primary cancer as compared with the general population. There were excesses in breast cancer, colorectal cancer, leukaemia, bladder cancer and possibly lung cancer.

Little is known about the aetiology and epidemiology of PFTC. Its aetiology is largely unknown but may be similar to that of ovarian carcinoma, since they both arise from the Müllerian duct. Previous studies have suggested that nulliparous women have an

increased risk of PFTC, as for ovarian and breast cancer.[1,21,22] There are earlier studies reporting a concomitant presentation of breast cancer, other gynaecological cancers and colon cancer among patients with PFTC,[2,12,23,24] suggested to reflect their similar hormone responsiveness.[24] First degree relatives of 44 PFTC cases had a suggestion of an increase in risk of ovarian cancer (RR = 2.2, 95% CI 0.4–6.3) and of early-onset breast cancer (RR = 2.4, 95% CI 0.6–6.1)[14]; germline BRCA1 mutations were found in 5 (11%) patients with PFTC and BRCA2 mutations in 2 (5%) patients. In comparison, out of unselected ovarian patients 3.5% were found to have BRCA1 mutations[13] and the prevalence of BRCA1 or BRCA2 mutations in the general population is 0.1%–0.2%.[15] Brose *et al*. reported a cumulative risk of 3.0% (95% CI 1.3–4.7%) for PFTC among BRCA1 carriers as compared with 0.025% in the general population.[16] Other reports have confirmed an increased risk of PFTC in BRCA1 or BRCA2 mutation carriers.[25–28] A population-based study from Sweden confirmed a very high risk (SIR 93, 95% CI 55–146) of PFTC in Swedish families with both breast and ovarian cancer.[29] In families with a case of breast cancer diagnosed before the age of 35 the SIR of PFTC was 5.5 (95% CI 1.0–16). In our study the excess risk of breast cancer became apparent more than 10 years after the PFTC diagnosis and the SIR was not highest in the youngest age groups, findings that appear unlikely to be explained by genetic susceptibility. The latency would fit better with a hypothesis of an effect of ionising radiation.[30]

Studies have advocated either pelvic or whole abdominal radiotherapy for treatment of PFTC, but because of low efficacy and a high rate of serious complications this should no longer be used except for palliation of specific symptoms.[2,8,31–33] The total doses used in the pelvic or total abdominal radiotherapy have ranged from 25 to 70 Gy (median 50.0 Gy).[34] There are no studies on the effect of radiation therapy, used as a treatment for PFTC, on breast or other second cancer risk. On the basis of studies concerning second malignancies among survivors of ovarian cancer[35] the risk effect of radiation therapy on PFTC should be low. The dose delivered to the breast during whole abdominal radiation therapy for PFTC should be similar to the dose delivered to the contralateral breast from tangential field treatments of the breast cancer. In our data the excess of breast cancer, bladder cancer, colorectal cancer and leukaemia could be in part late effects of pelvic or abdominal radiation.

Studies on late effects of chemotherapy treatments for cancer have revealed an increased risk of second primary leukaemia, mainly acute myeloid leukaemia.[36] The relative risk (RR) of leukaemia after platinum-based chemotherapy for ovarian cancer was 4.0 (95% CI 1.4–11).[37] For carboplatin the relative risk was 6.5 (95% CI 1.2–37) and for cisplatin 3.3 (95% CI 1.1–9.4). The effect was dose related, with the RR reaching 7.6 (95% CI 2.3–25) at doses of 1,000 mg or more of platinum. The platinum-based chemotherapy has been the main adjuvant therapy for PFTC and could therefore explain the high rates of nonlymphoid leukaemia after PFTC. Since the 1990s taxanes have been combined with platinum-based drugs in the treatment of PFTC, especially in advanced disease with a residual tumor after the operation. There are case reports of secondary acute myeloid leukaemias after the treatment with taxanes.[38,39]

All cases of nonlymphoid leukaemia and the majority of excess cases of breast cancer were diagnosed among PFTC patients treated after 1975, *i.e*., the hypothesis that the elevated SIRs are due to earlier cancer treatment protocols seems not to hold. There were no nonlymphoid leukaemia cases immediately after the diagnosis of the PFTC, but only during the 2nd to 10th year after the PFTC, which may indicate an effect of platinum-based chemotherapy.[37] The overall excess of breast cancer, colorectal cancer and bladder cancer may reflect an effect of treatments with radiotherapy and/or chemotherapy.

There were 2 cases of cervical cancer and 2 endometrial cancers diagnosed within 1 year after the diagnosis of PFTC. These may be related to the additional diagnostic and treatment activities due to the PFTC.

Tobacco-smoking is a strong established risk factor for lung cancer and bladder cancer; it has been estimated that 79% of lung cancers and 32% bladder cancers around the year 2000 among women in the Nordic countries would be avoided if cigarette smoking were eliminated.[40] The raised SIRs for those cancers as second primary cancers after PFTC suggest that smoking may also have a role in the aetiology of PFTC.

Our results are based on records collected from 13 cancer registries with different registration practises in multiple cancer coding. Misclassification of metastases as new primary cancers does not seem to have been a problem, since we observed reduced risk estimates for sites frequently exposed to metastasis, such as liver, bone and brain. This may reflect a conservative coding principle: a cancer is not accepted as new primary cancer if there is any doubt that it could be a metastasis.

The conclusion of this study is that history of a PFTC has an effect on the subsequent risk of breast, colorectal, bladder and lung cancers and nonlymphoid leukaemia. Although with the largest PFTC patient cohort ever collected for this kind of study, due to the rarity of this cancer and the lack of individual data on risk factors and treatment it is difficult to determine how much of the excess risks might be associated with shared genetic or life habit factors and how much is related to treatment of the PFTC.

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